

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
1 May 2003 (01.05.2003)

PCT

(10) International Publication Number
WO 03/035615 A2

- (51) International Patent Classification⁷: **C07D**
- (21) International Application Number: **PCT/US02/33920**
- (22) International Filing Date: 21 October 2002 (21.10.2002)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
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- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 03/035615 A2

(54) Title: **TYROSINE KINASE INHIBITORS**

(57) Abstract: The present invention relates to compounds that are capable of inhibiting, modulating and/or regulating signal transduction of both receptor-type and non-receptor type tyrosine kinases. The compounds of the instant invention possess a core structure that comprises a 2-carboxy pyrrole. The present invention is also related to the pharmaceutically acceptable salts, hydrates and stereoisomers of these compounds.

TITLE OF THE INVENTION

TYROSINE KINASE INHIBITORS

BACKGROUND OF THE INVENTION

5 Protein kinases (PKs) are enzymes that catalyze the phosphorylation of hydroxy groups on tyrosine, serine and threonine residues of proteins. The consequences of this seemingly simple activity are staggering; cell growth, differentiation and proliferation; i.e., virtually all aspects of cell life, in one way or another depend on PK activity. Furthermore, abnormal PK activity has been related
10 to a host of disorders, ranging from relatively non life-threatening diseases such as psoriasis to extremely virulent diseases such as glioblastoma (brain cancer). PKs can be broken into two classes, the protein tyrosine kinases (PTKs) and the serine-threonine kinases (STKs).

Certain growth factor receptors exhibiting PK activity are known as
15 receptor tyrosine kinases (RTKs). They comprise a large family of transmembrane receptors with diverse biological activity. As present, at least nineteen (19) distinct subfamilies of RTKs have been identified. One RTK subfamily contains the insulin receptor (IR), insulin-like growth factor I receptor (IGF-1R) and insulin receptor related receptor (IRR). IR and IGF-1R interact with insulin, IGF-I and IGF-II to
20 activate a hetero-tetramer composed of two entirely extracellular glycosylated α subunits and two β subunits which cross the cell membrane and which contain the tyrosine kinase domain. The Insulin-like Growth Factor-1 Receptor (IGF-1R), and its ligands, IGF-1 and IGF-2, are abnormally expressed in numerous tumors, including, but not limited to, breast, prostate, thyroid, lung, hepatoma, colon, brain,
25 neuroendocrine, and others.

A more complete listing of the known RTK subfamilies is described in Plowman et al., KN&P, 1994, 7(6) :334-339 which is incorporated by reference, including any drawings, as if fully set forth herein.

In addition to the RTKs, there also exists a family of entirely
30 intracellular PTKs called "non-receptor tyrosine kinases" or "cellular tyrosine

kinases.” This latter designation, abbreviated “CTK”, will be used herein. CTKs do not contain extracellular and transmembrane domains. At present, over 24 CTKs in 11 subfamilies (Src, Frk, Btk, Csk, Abl, Zap70, Fes, Fps, Fak, Jak and Ack) have been identified. The Src subfamily appears so far to be the largest group of CTKs and includes Src, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr and Yrk. For a more detailed discussion of CTKs, see Bolen, *Oncogene*, 1993, 8:2025-2031, which is incorporated by reference, including any drawings, as if fully set forth herein.

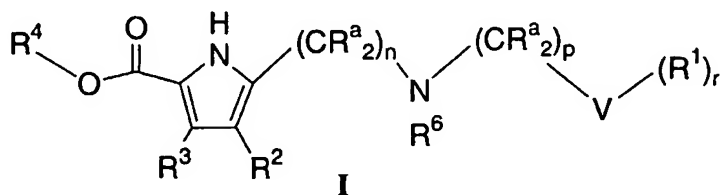
RTKs, CTKs and STKs have all been implicated in a host of pathogenic conditions including significantly, cancer. Other pathogenic conditions which have been associated with PTKs include, without limitation, psoriasis, hepatic cirrhosis, diabetes, atherosclerosis, angiogenesis, restenosis, ocular diseases, rheumatoid arthritis and other inflammatory disorders, autoimmune diseases and a variety of renal disorders.

SUMMARY OF THE INVENTION

The present invention relates to compounds that are capable of inhibiting, modulating and/or regulating signal transduction of both receptor-type and non-receptor type tyrosine kinases. The compounds of the instant invention possess a core structure that comprises a 2-carboxy pyrrole. The present invention is also related to the pharmaceutically acceptable salts, hydrates and stereoisomers of these compounds.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention are useful in the inhibition of kinases and are illustrated by a compound of Formula I:



wherein

V is selected from

- 1) C₁-C₁₀ alkyl,
- 5 2) aryl,
- 3) heterocycle,
- 4) C₃-C₁₀ cycloalkyl, and
- 5) -C(O);

10 R^a is independently selected from

- 1) H,
- 2) OR⁷,
- 3) unsubstituted or substituted C₁-C₁₀ alkyl
- 4) unsubstituted or substituted aryl, and
- 15 5) unsubstituted or substituted heterocycle;

R^b is independently selected from

- 1) H,
- 2) OR⁷,
- 20 3) unsubstituted or substituted C₁-C₁₀ alkyl,
- 4) unsubstituted or substituted aryl, and
- 5) unsubstituted or substituted heterocycle;

R¹ is independently selected from

- 25 1) H,
- 2) unsubstituted or substituted C₁-C₁₀ alkyl,
- 3) unsubstituted or substituted C₃-C₁₀ cycloalkyl,
- 4) unsubstituted or substituted aryl,
- 5) unsubstituted or substituted heterocycle,

- 6) OR^7 ,
 7) $C(O)R^7$,
 8) $C(O)OR^7$,
 9) $C(O)N(R^7)_2$,
 5 10) $N(R^7)_2$,
 11) halo, and
 12) $-S(O)_2N(R^5)_2$;

R^2 is selected from

- 10 1) unsubstituted or substituted C_1 - C_{10} alkyl,
 2) $-C(O)OR^7$,
 3) unsubstituted or substituted aryl,
 4) $-(CR^{b2})_nN(R^7)_2$,
 5) $-C(O)N(R^7)_2$,
 15 6) $-C(O)NHR^7OR^7$,
 7) $-C(O)NH(CR^{b2})_qR^7$,
 8) $-C(O)NHR^7NHC(O)R^7$,
 9) $-C(O)NHR^7S(O)_2OR^7$,
 10) $(CR^{b2})_nOR^7$, and
 20 11) $-C(O)NH(CR^{b2})_qC(O)N(R^7)_2$;

R^3 is selected from

- 1) H,
 2) unsubstituted or substituted C_1 - C_{10} alkyl,
 25 3) unsubstituted or substituted aralkyl
 4) unsubstituted or substituted aryl,
 5) unsubstituted or substituted heterocycle, and
 6) unsubstituted or substituted heterocyclalkyl;

R⁴ is selected from

- 1) unsubstituted or substituted C₁-C₁₀ alkyl,
- 2) unsubstituted or substituted aryl,
- 5 3) unsubstituted or substituted aralkyl, and
- 4) unsubstituted or substituted heterocycle;

R⁵ is independently selected from

- 1) H,
- 10 2) unsubstituted or substituted C₁-C₁₀ alkyl,
- 3) unsubstituted or substituted aryl, and
- 4) unsubstituted or substituted heterocycle;

R⁶ is independently selected from

- 15 1) H,
- 2) unsubstituted or substituted C₁-C₁₀ alkyl,
- 3) unsubstituted or substituted aryl,
- 4) unsubstituted or substituted heterocycle,
- 5) OR⁷,
- 20 6) unsubstituted or substituted aralkyl, and
- 7) unsubstituted or substituted heterocyclalkyl;

R⁷ is independently selected from

- 1) H,
- 25 2) unsubstituted or substituted C₁-C₁₀ alkyl,
- 3) unsubstituted or substituted aralkyl,
- 4) unsubstituted or substituted aryl,
- 5) unsubstituted or substituted heterocycle, and
- 6) unsubstituted or substituted heterocyclalkyl;

- n is 0 to 6,
p is 0 to 6,
q is 0 to 5, and
5 r is 0 to 6;

or a pharmaceutically acceptable salt or stereoisomer thereof.

A second embodiment of the instant invention is a compound of
10 Formula I, as described above, wherein:

R⁴ is selected from

- 1) unsubstituted or substituted C₁-C₁₀ alkyl, and
- 2) unsubstituted or substituted aryl;

15

or a pharmaceutically acceptable salt or stereoisomer thereof.

A further embodiment is a compound as described in the second
embodiment above, wherein:

20

R¹ is independently selected from

- 1) H,
- 2) unsubstituted or substituted C₁-C₁₀ alkyl,
- 3) unsubstituted or substituted C₃-C₁₀ cycloalkyl,
- 25 4) OR⁷,
- 5) C(O)R⁷,
- 6) C(O)OR⁷,
- 7) C(O)N(R⁷)₂,
- 8) N(R⁷)₂,

- 9) halo, and
10) $-S(O)_2N(R^5)_2$;

- n is 0 to 2,
5 p is 0 to 4,
q is 0 to 3, and
r is 0 to 4,

or a pharmaceutically acceptable salt or stereoisomer thereof.

10

Examples of compounds of the instant invention include

2-tert-butyl 4-ethyl 3-benzyl-5-[(4-chlorophenyl)amino]methyl]-1H-pyrrole-2,4-dicarboxylate;

- 15 [5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-[(5-oxopyrrolidin-2-yl)methyl]methanaminium trifluoroacetate;

[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-(1H-indol-2-yl)methyl]methanaminium trifluoroacetate;

20

N-{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-3,4-dichlorobenzenaminium trifluoroacetate;

N-{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-4-

- 25 methylbenzenaminium trifluoroacetate;

N-{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-4-hydroxybenzenaminium trifluoroacetate;

- N-{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-4-methoxybenzenaminium trifluoroacetate;
- N-{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-4-chloro-N-methylbenzenaminium trifluoroacetate;
- 2-([5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl)ammonio)methyl]-6-methylpyridinium bis(trifluoroacetate);
- 10 3-([5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl)ammonio)methyl]-5-cyclopropyl-1H-pyrazol-1-ium bis(trifluoroacetate);
- [5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-[(3,5-dimethyl-1H-pyrazol-4-yl)methyl]methanaminium trifluoroacetate;
- 15 [5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-[(5-phenyl-1,3,4-oxadiazol-2-yl)methyl]methanaminium trifluoroacetate;
- 2-([5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl)ammonio)methyl]-1H-imidazol-1-ium bis(trifluoroacetate);
- 20 5-([5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl)ammonio)methyl]-3-methyl-4H-1,2,4-triazole-1,4-dium tris(trifluoroacetate);
- 25 6-([5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl)ammonio)methyl]-2-methylimidazo[2,1-b][1,3]thiazol-7-ium bis(trifluoroacetate);
- 2-([5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl)ammonio)methyl]-4-methyl-1H-imidazol-3-ium bis(trifluoroacetate);
- 30

- 2-[[{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl} ammonio)methyl]-1-methyl-1H-imidazol-3-ium bis(trifluoroacetate);
- 5 [5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-[(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl]methanaminium trifluoroacetate;
- 5-[[{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl} ammonio)methyl]-1H-1,2,4-triazol-1-ium bis(trifluoroacetate);
- 10 6-[[{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl} ammonio)methyl]imidazo[2,1-b][1,3]thiazol-4-ium bis(trifluoroacetate);
- 2-[[{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl} ammonio)methyl]-5-chloro-3H-benzimidazol-1-ium bis(trifluoroacetate);
- 15 [5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-[(4-oxo-3,4-dihydrophthalazin-1-yl)methyl]methanaminium trifluoroacetate;
- [5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-(1H-indol-6-yl)methyl]methanaminium trifluoroacetate;
- 20 [5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-[(4-methyl-1,3-thiazol-2-yl)methyl]methanaminium trifluoroacetate;
- 25 2-[[{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl} ammonio)methyl]-8-methylimidazo[1,2-a]pyridin-4-ium bis(trifluoroacetate);
- 2-[[{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl} ammonio)methyl]-3H-benzimidazol-1-ium bis(trifluoroacetate);
- 30

N-{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-3-methylbenzenaminium trifluoroacetate;

5 N-{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-4-isopropylbenzenaminium trifluoroacetate;

N-{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-4-ethylbenzenaminium trifluoroacetate;

10 N-{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-3,5-dimethylbenzenaminium trifluoroacetate;

N-{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-3,4-dimethoxybenzenaminium trifluoroacetate;

15 2-[2-([5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl)ammonio)ethyl]pyridinium bis(trifluoroacetate);

20 [5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-[(1-methyl-1H-pyrazol-4-yl)methyl]methanaminium trifluoroacetate;

N-{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-4-ethoxybenzenaminium trifluoroacetate;

25 N-{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-3,4-dimethylbenzenaminium trifluoroacetate;

N-{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-1,3-benzodioxol-5-aminium trifluoroacetate;

30

N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl)methyl}-4-isopropoxybenzenaminium trifluoroacetate;

4-(((5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl)methyl) ammonio)methyl]-1,3-thiazol-3-ium bis(trifluoroacetate);

5-(((5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl)methyl) ammonio)methyl]-1,3-thiazol-3-ium bis(trifluoroacetate);

10 2-(((5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl)methyl) ammonio)methyl]-1,3-thiazol-3-ium bis(trifluoroacetate);

[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-(isoxazol-5-ylmethyl)methanaminium trifluoroacetate;

15 [5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-[(1,5-dimethyl-1H-pyrazol-4-yl)methyl]methanaminium trifluoroacetate;

N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl)methyl}-4-tert-butylbenzenaminium trifluoroacetate;

2-tert-butyl 4-ethyl 5-({[4-(dimethylamino)phenyl]amino)methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate bis(trifluoroacetate);

25 N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl)methyl}-2-methylbenzenaminium trifluoroacetate;

N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl)methyl}-2-methoxybenzenaminium trifluoroacetate;

30

N-{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-4-propylbenzenaminium trifluoroacetate;

5 N-{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-2,5-dimethoxybenzenaminium trifluoroacetate;

N-{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-4-butylbenzenaminium trifluoroacetate;

10 N-{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-3-hydroxy-4-methoxybenzenaminium trifluoroacetate;

N-{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-1H-indol-4-aminium trifluoroacetate;

15 N-{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-1H-indol-6-aminium trifluoroacetate;

20 N-{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-3-methoxypropan-1-aminium trifluoroacetate;

N-{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}ethanaminium trifluoroacetate;

25 N-{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}butan-1-aminium trifluoroacetate;

N-{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-3-methoxybenzenaminium trifluoroacetate;

30

N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl)methyl}-3-carboxypropan-1-aminium trifluoroacetate;

5 [5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-methylmethanaminium trifluoroacetate;

N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl)methyl}-2-methylpropan-1-aminium trifluoroacetate;

10 N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl)methyl}pentan-1-aminium trifluoroacetate;

2-(aminosulfonyl)-N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl)methyl}ethanaminium trifluoroacetate;

15 [5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-(1H-pyrrol-2-yl)methylmethanaminium trifluoroacetate;

20 N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl)methyl}-4-chlorobenzenaminium chloride;

N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl)methyl}-3-chlorobenzenaminium chloride;

25 N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl)methyl}-2-chlorobenzenaminium chloride;

3-bromo-N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl)methyl}benzenaminium chloride;

30

- 2-bromo-N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl}methyl}benzenaminium chloride;
- 5 N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl}methyl}-4-fluorobenzenaminium chloride;
- N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl}methyl}-3-fluorobenzenaminium chloride;
- 10 N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl}methyl}-2-fluorobenzenaminium chloride;
- 3-({[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}ammonio)pyridinium dichloride;
- 15 2-({[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}ammonio)-5-chloropyridinium dichloride;
- 4-bromo-N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl}methyl}benzenaminium chloride;
- 20 2-tert-butyl 4-methyl 3-ethyl-5-{{(4-methoxyphenyl)amino}methyl}-1H-pyrrole-2,4-dicarboxylate;
- 25 N-{{5-(tert-butoxycarbonyl)-4-ethyl-3-(methoxycarbonyl)-1H-pyrrol-2-yl}methyl}-4-pentylbenzenaminium trifluoroacetate;
- N-{{5-(tert-butoxycarbonyl)-4-ethyl-3-(methoxycarbonyl)-1H-pyrrol-2-yl}methyl}-1,1'-biphenyl-4-aminium trifluoroacetate;
- 30

- N- {[5-(tert-butoxycarbonyl)-4-ethyl-3-(methoxycarbonyl)-1H-pyrrol-2-yl]methyl}-
3,4,5-trimethoxybenzenaminium trifluoroacetate;
- 3-[4-({ [5-(tert-butoxycarbonyl)-4-ethyl-3-(methoxycarbonyl)-1H-pyrrol-2-yl]methyl }
5 ammonio)phenyl]-5-methyl-4H-1,2,4-triazol-4-ium bis(trifluoroacetate);
- [5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N- {[(2R)-5-
oxopyrrolidin-2-yl]methyl } methanaminium trifluoroacetate;
- 10 diethyl 5- {[(4-chlorophenyl)amino]methyl }-3-methyl-1H-pyrrole-2,4-dicarboxylate;
- N-benzyl[3,5-bis(ethoxycarbonyl)-4-methyl-1H-pyrrol-2-yl]methanaminium chloride;
- [3,5-bis(ethoxycarbonyl)-4-methyl-1H-pyrrol-2-yl]-N-(pyridin-2-ylmethyl)
15 methanaminium chloride;
- [3,5-bis(ethoxycarbonyl)-4-methyl-1H-pyrrol-2-yl]-N-(2-chlorobenzyl)
methanaminium chloride;
- 20 [3,5-bis(ethoxycarbonyl)-4-methyl-1H-pyrrol-2-yl]-N-(3-chlorobenzyl)
methanaminium chloride;
- [3,5-bis(ethoxycarbonyl)-4-isopropyl-1H-pyrrol-2-yl]-N-(pyridin-2-ylmethyl)
methanaminium chloride;
- 25 [5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-(pyridin-2-
ylmethyl)methanaminium chloride;
- N- {[3-[(benzyloxy)carbonyl]-5-(tert-butoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]
30 methyl }-4-methoxybenzenaminium trifluoroacetate;

- N-{[5-(tert-butoxycarbonyl)-3-carboxy-4-ethyl-1H-pyrrol-2-yl]methyl}-4-methoxybenzenaminium trifluoroacetate;
- 5 N-[(5-(tert-butoxycarbonyl)-4-ethyl-3-[(2-hydroxyethyl)amino]carbonyl)-1H-pyrrol-2-yl]methyl]-4-methoxybenzenaminium trifluoroacetate;
- N-({5-(tert-butoxycarbonyl)-4-ethyl-3-[(ethylamino)carbonyl]-1H-pyrrol-2-yl}methyl)-4-methoxybenzenaminium trifluoroacetate;
- 10 2-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-[(4-methoxyphenyl)ammonio]methyl)-1H-pyrrol-3-yl]carbonyl}amino)methylpyridinium bis(trifluoroacetate);
- 4-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-[(4-methoxyphenyl)ammonio]methyl)-1H-pyrrol-3-yl]carbonyl}amino)methylpyridinium bis(trifluoroacetate);
- 15 N-({5-(tert-butoxycarbonyl)-4-ethyl-3-[(propylamino)carbonyl]-1H-pyrrol-2-yl}methyl)-4-methoxybenzenaminium trifluoroacetate;
- 20 N-{[5-(tert-butoxycarbonyl)-4-ethyl-3-({[(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl]amino}carbonyl)-1H-pyrrol-2-yl]methyl}-4-methoxybenzenaminium trifluoroacetate;
- 2-2-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-[(4-methoxyphenyl)ammonio]methyl)-1H-pyrrol-3-yl]carbonyl}amino)ethylpyridinium bis(trifluoroacetate);
- 25 2-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-[(4-methoxyphenyl)ammonio]methyl)-1H-pyrrol-3-yl]carbonyl}amino)methyl)-1H-imidazol-1-ium bis(trifluoroacetate);

- N-{[5-(tert-butoxycarbonyl)-4-ethyl-3-({[(5-oxopyrrolidin-2-yl)methyl]amino} carbonyl)-1H-pyrrol-2-yl)methyl}-4-methoxybenzenaminium trifluoroacetate;
- 3-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-1H-pyrrol-3-yl)carbonyl]amino}methyl)pyridinium bis(trifluoroacetate);
- 5 2-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-1H-pyrrol-3-yl)carbonyl]amino}methyl)-3H-benzimidazol-1-ium bis(trifluoroacetate);
- 10 N-[(5-(tert-butoxycarbonyl)-4-ethyl-3-{{(isoxazol-3-yl)methyl}amino}carbonyl)-1H-pyrrol-2-yl)methyl]-4-methoxybenzenaminium trifluoroacetate;
- N-{[3-({[2-(acetylamino)ethyl]amino} carbonyl)-5-(tert-butoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl)methyl]-4-methoxybenzenaminium trifluoroacetate};
- 15 N-{[5-(tert-butoxycarbonyl)-4-ethyl-3-({[(5-methyl-1,3,4-oxadiazol-2-yl)methyl] amino}carbonyl)-1H-pyrrol-2-yl)methyl]-4-methoxybenzenaminium trifluoroacetate};
- N-[(5-(tert-butoxycarbonyl)-4-ethyl-3-{{(2-sulfoethyl)amino}carbonyl)-1H-pyrrol-2-yl)methyl]-4-methoxybenzenaminium trifluoroacetate;
- 20 N-{[3-{{(benzylamino)carbonyl}-5-(tert-butoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl} methyl]-4-methoxybenzenaminium trifluoroacetate};
- 25 3-(2-{{[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-1H-pyrrol-3-yl)carbonyl]amino}ethyl)-5-methyl-4H-1,2,4-triazol-4-ium bis(trifluoroacetate);
- 4-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-1H-pyrrol-3-yl)carbonyl]amino}methyl)-2-methyl-1,3-thiazol-3-ium bis(trifluoroacetate);
- 30

- 4-(2-{{(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-1H-pyrrol-3-yl)carbonyl}amino}ethyl)-1H-pyrazol-1-ium bis(trifluoroacetate);
- 5 N-{{(5-(tert-butoxycarbonyl)-4-ethyl-3-{{(1H-indol-6-ylmethyl)amino}carbonyl}-1H-pyrrol-2-yl)methyl}}-4-methoxybenzenaminium trifluoroacetate;
- 6-({{(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-1H-pyrrol-3-yl)carbonyl}amino}methyl)-2-methylimidazo[2,1-b][1,3]thiazol-7-ium bis(trifluoroacetate);
- 10 5-({{(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-1H-pyrrol-3-yl)carbonyl}amino}methyl)-3-methyl-4H-1,2,4-triazole-1,4-diium tris(trifluoroacetate);
- 15 4-({{(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-1H-pyrrol-3-yl)carbonyl}amino}methyl)-1-methyl-1H-pyrazol-2-ium bis(trifluoroacetate);
- N-{{(5-(tert-butoxycarbonyl)-4-ethyl-3-({{(1-methyl-5-oxopyrrolidin-2-yl)methyl}amino}carbonyl)-1H-pyrrol-2-yl)methyl}}-4-methoxybenzenaminium trifluoroacetate;
- 20 2-(2-{{(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-1H-pyrrol-3-yl)carbonyl}amino}ethyl)-5-methoxy-3H-benzimidazol-1-ium bis(trifluoroacetate);
- 25 5-(2-{{(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-1H-pyrrol-3-yl)carbonyl}amino}ethyl)-1H-1,2,4-triazol-1-ium bis(trifluoroacetate);
- 2-({{(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-1H-pyrrol-3-yl)carbonyl}amino}methyl)-1-methyl-1H-imidazol-
- 30 3-ium bis(trifluoroacetate);

- 6-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-1H-pyrrol-3-yl)carbonyl]amino}methyl)-2,3-dihydroimidazo[2,1-b][1,3]thiazol-4-ium bis(trifluoroacetate);
- 5 2-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-1H-pyrrol-3-yl)carbonyl]amino}methyl)-4-methyl-1H-imidazol-3-ium bis(trifluoroacetate);
- 10 2-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-1H-pyrrol-3-yl)carbonyl]amino}methyl)-8-methylimidazo[1,2-a]pyridin-4-ium bis(trifluoroacetate);
- 15 3-(1-{{(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-1H-pyrrol-3-yl)carbonyl]amino}ethyl)-5-methyl-4H-1,2,4-triazol-4-ium bis(trifluoroacetate);
- 20 2-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-1H-pyrrol-3-yl)carbonyl]amino}methyl)quinolinium bis(trifluoroacetate);
- 2-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-1H-pyrrol-3-yl)carbonyl]amino}methyl)-6-methylpyridinium bis(trifluoroacetate);
- 25 N-{{(5-(tert-butoxycarbonyl)-4-ethyl-3-({[(4-methyl-1,3-thiazol-2-yl)methyl]amino}carbonyl)-1H-pyrrol-2-yl)methyl}-4-methoxybenzenaminium trifluoroacetate;
- 30 3-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-1H-pyrrol-3-yl)carbonyl]amino}methyl)-6,7-dihydro-5H-cyclopenta[b]pyridinium bis(trifluoroacetate);

3-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-1H-pyrrol-3-yl)carbonyl]amino}methyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridinium bis(trifluoroacetate);

- 5 N-{{[5-(tert-butoxycarbonyl)-4-ethyl-3-{{[2-(4-methyl-1,3-thiazol-5-yl)ethyl]amino}carbonyl}-1H-pyrrol-2-yl]methyl}-4-methoxybenzenaminium trifluoroacetate;

3-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-1H-pyrrol-3-yl)carbonyl]amino}methyl)-1-methylpiperidinium bis(trifluoroacetate);

10

4-(2-{{[5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-1H-pyrrol-3-yl)carbonyl]amino}-1-pyridinium-4-ylethyl)morpholin-4-ium tris(trifluoroacetate);

- 15 4-(2-{{[5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-1H-pyrrol-3-yl)carbonyl]amino}-1-pyridinium-3-ylethyl)morpholin-4-ium tris(trifluoroacetate);

- 20 N-{{[5-(tert-butoxycarbonyl)-4-ethyl-3-{{[5-fluoro-2-oxo-2,3-dihydro-1H-indol-3-yl]methyl]amino}carbonyl}-1H-pyrrol-2-yl]methyl}-4-methoxybenzenaminium trifluoroacetate;

- 25 3-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-1H-pyrrol-3-yl)carbonyl]amino}methyl)-5-cyclopropyl-1H-pyrazol-1-ium bis(trifluoroacetate);

2-{{[[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl](hydroxy)ammonio}methyl}pyridinium bis(trifluoroacetate);

2-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{[(4-methoxyphenyl)ammonio]methyl}}-1H-pyrrol-3-yl)carbonyl]oxy}methyl)pyridinium bis(trifluoroacetate);

5 N-{{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-(2-phenylethyl)-1H-pyrrol-2-yl]methyl}}-4-chlorobenzenaminium trifluoroacetate;

2-amino-N-{{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}}glycinamide trifluoroacetate;

10 N-{{[5-(tert-butoxycarbonyl)-4-ethyl-3-glycinamide-1H-pyrrol-2-yl]methyl}}-4-methoxybenzenaminium trifluoroacetate;

or a stereoisomer thereof.

15 Further examples of compounds of the instant invention include:

2-tert-butyl 4-ethyl 3-ethyl-5-({[(5-oxopyrrolidin-2-yl)methyl]amino}methyl)-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-({[(1H-indol-2-yl)methyl]amino}methyl)-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-({[(3,4-dichlorophenyl)amino]methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-({[(4-methylphenyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-({[(4-hydroxyphenyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-({[(4-methoxyphenyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-({[(4-chlorophenyl)(methyl)amino]methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-({[(6-methylpyridin-2-yl)methyl]amino}methyl)-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-({[(5-cyclopropyl-1H-pyrazol-3-yl)methyl]amino}methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-({[(3,5-dimethyl-1H-pyrazol-4-yl)methyl]amino}methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-({[(1H-indol-2-yl)methyl]amino}methyl)-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-({[(1H-imidazol-2-yl)methyl]amino}methyl)-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-({[(5-methyl-4H-1,2,4-triazol-3-yl)methyl]amino}methyl)-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-({[(2-methylimidazo[2,1-b][1,3]thiazol-6-yl)methyl]amino}methyl)-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-({[(4-methyl-1H-imidazol-2-yl)methyl]amino}methyl)-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-({[(1-methyl-1H-imidazol-2-yl)methyl]amino}methyl)-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-({[(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl]amino}methyl)-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-({[(1H-1,2,4-triazol-5-yl)methyl]amino}methyl)-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-({[(imidazo[2,1-b][1,3]thiazol-6-yl)methyl]amino}methyl)-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-({[(6-chloro-1H-benzimidazol-2-yl)methyl]amino}methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-({[(4-oxo-3,4-dihydrophthalazin-1-yl)methyl]amino}methyl)-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-({[(1H-indol-6-yl)methyl]amino}methyl)-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-({[(4-methyl-1,3-thiazol-2-yl)methyl]amino}methyl)-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-({[(8-methylimidazo[1,2-a]pyridin-2-yl)methyl]amino}methyl)-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-({[(1H-benzimidazol-2-yl)methyl]amino}methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-({[(3-methylphenyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-({[(4-isopropylphenyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-({[(4-ethylphenyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-({[(3,5-dimethylphenyl)amino]methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-({[(3,4-dimethoxyphenyl)amino]methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-({[(2-pyridin-2-ylethyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-({[(1-methyl-1H-pyrazol-4-yl)methyl]amino}methyl)-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-({[(4-ethoxyphenyl)amino]methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-({[(3,4-dimethylphenyl)amino]methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-[(1,3-benzodioxol-5-ylamino)methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-({[(4-isopropoxyphenyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-({[(1,3-thiazol-4-yl)methyl]amino}methyl)-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-[[[(1,3-thiazol-5-ylmethyl)amino]methyl]-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-[[[(1,3-thiazol-2-ylmethyl)amino]methyl]-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-[[[(isoxazol-5-ylmethyl)amino]methyl]-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-([[(1,5-dimethyl-1H-pyrazol-4-yl)methyl]amino)methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-[[[(4-tert-butylphenyl)amino]methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-([[(4-(dimethylamino)phenyl)amino]methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-[[[(2-methylphenyl)amino]methyl]-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-[[[(2-methoxyphenyl)amino]methyl]-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-[[[(4-propylphenyl)amino]methyl]-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-[[[(2,5-dimethoxyphenyl)amino]methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-[[[(4-butylphenyl)amino]methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-[[[(3-hydroxy-4-methoxyphenyl)amino]methyl]-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-[(1H-indol-4-ylamino)methyl]-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-[(1H-indol-6-ylamino)methyl]-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-[[[(3-methoxypropyl)amino]methyl]-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-[(ethylamino)methyl]-1H-pyrrole-2,4-dicarboxylate;
2-tert-butyl 4-ethyl 5-[(butylamino)methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
2-tert-butyl 4-ethyl 3-ethyl-5-[[(3-methoxyphenyl)amino]methyl]-1H-pyrrole-2,4-dicarboxylate;
4-([5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl)amino)butanoic acid;
2-tert-butyl 4-ethyl 3-ethyl-5-[(methylamino)methyl]-1H-pyrrole-2,4-dicarboxylate;
2-tert-butyl 4-ethyl 3-ethyl-5-[(isobutylamino)methyl]-1H-pyrrole-2,4-dicarboxylate;
2-tert-butyl 4-ethyl 3-ethyl-5-[(pentylamino)methyl]-1H-pyrrole-2,4-dicarboxylate;
2-tert-butyl 4-ethyl 5-([2-(aminosulfonyl)ethyl]amino)methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
2-tert-butyl 4-ethyl 3-ethyl-5-([(1H-pyrrol-2-yl)methyl]amino)methyl)-1H-pyrrole-2,4-dicarboxylate;
2-tert-butyl 4-ethyl 5-[[(4-chlorophenyl)amino]methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
2-tert-butyl 4-ethyl 5-[[(3-chlorophenyl)amino]methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
2-tert-butyl 4-ethyl 5-[[(2-chlorophenyl)amino]methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
2-tert-butyl 4-ethyl 5-[[(3-bromophenyl)amino]methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
2-tert-butyl 4-ethyl 5-[[(2-bromophenyl)amino]methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
2-tert-butyl 4-ethyl 3-ethyl-5-[[(4-fluorophenyl)amino]methyl]-1H-pyrrole-2,4-dicarboxylate;
2-tert-butyl 4-ethyl 3-ethyl-5-[[(3-fluorophenyl)amino]methyl]-1H-pyrrole-2,4-dicarboxylate;
2-tert-butyl 4-ethyl 3-ethyl-5-[[(2-fluorophenyl)amino]methyl]-1H-pyrrole-2,4-dicarboxylate;
2-tert-butyl 4-ethyl 3-ethyl-5-[(pyridin-3-ylamino)methyl]-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-[[[(5-chloropyridin-2-yl)amino]methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-[[[(4-bromophenyl)amino]methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-methyl 3-ethyl-5-[[[(4-pentylphenyl)amino]methyl]-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-methyl 5-[(1,1'-biphenyl-4-ylamino)methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-methyl 3-ethyl-5-[[[(3,4,5-trimethoxyphenyl)amino]methyl]-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-methyl 3-ethyl-5-[[[(4-(5-methyl-4H-1,2,4-triazol-3-yl)phenyl)amino]methyl]-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-[[[(2R)-5-oxopyrrolidin-2-yl]methyl]amino]methyl]-1H-pyrrole-2,4-dicarboxylate;

diethyl 5-[(benzylamino)methyl]-3-methyl-1H-pyrrole-2,4-dicarboxylate;

diethyl 3-methyl-5-[[[(pyridin-2-ylmethyl)amino]methyl]-1H-pyrrole-2,4-dicarboxylate;

diethyl 5-[[[(2-chlorobenzyl)amino]methyl]-3-methyl-1H-pyrrole-2,4-dicarboxylate;

diethyl 5-[[[(3-chlorobenzyl)amino]methyl]-3-methyl-1H-pyrrole-2,4-dicarboxylate;

diethyl 3-isopropyl-5-[[[(pyridin-2-ylmethyl)amino]methyl]-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-[[[(pyridin-2-ylmethyl)amino]methyl]-1H-pyrrole-2,4-dicarboxylate;

4-benzyl 2-tert-butyl 3-ethyl-5-[[[(4-methoxyphenyl)amino]methyl]-1H-pyrrole-2,4-dicarboxylate;

5-(tert-butoxycarbonyl)-4-ethyl-2-[[[(4-methoxyphenyl)amino]methyl]-1H-pyrrole-3-carboxylic acid;

tert-butyl 3-ethyl-4-[[[(2-hydroxyethyl)amino]carbonyl]-5-[[[(4-methoxyphenyl)amino]methyl]-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-4-[(ethylamino)carbonyl]-5-[[[(4-methoxyphenyl)amino]methyl]-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-{{[(pyridin-2-ylmethyl)amino]carbonyl}}-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-{{[(pyridin-4-ylmethyl)amino]carbonyl}}-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-[(propylamino)carbonyl]}-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-{{[(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl]amino}carbonyl}}-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-{{[(2-pyridin-2-ylethyl)amino]carbonyl}}-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-4-{{[(1H-imidazol-2-ylmethyl)amino]carbonyl}-5-{{[(4-methoxyphenyl)amino]methyl}}-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-{{[(5-oxopyrrolidin-2-yl)methyl]amino}carbonyl}}-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-{{[(pyridin-3-ylmethyl)amino]carbonyl}}-1H-pyrrole-2-carboxylate;

tert-butyl 4-{{[(1H-benzimidazol-2-ylmethyl)amino]carbonyl}}-3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}}-1H-pyrrole-2-carboxylate

tert-butyl 3-ethyl-4-{{[(isoxazol-3-ylmethyl)amino]carbonyl}-5-{{[(4-methoxyphenyl)amino]methyl}}-1H-pyrrole-2-carboxylate;

tert-butyl 4-{{[2-(acetyl)amino]ethyl}amino}carbonyl)-3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}}-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-{{[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]amino}carbonyl}}-1H-pyrrole-2-carboxylate;

2-{{[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{[(4-methoxyphenyl)amino]methyl}}-1H-pyrrol-3-yl)carbonyl]amino}ethanesulfonic acid;

tert-butyl 4-[(benzylamino)carbonyl]-3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}}-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-{{[2-(5-methyl-4H-1,2,4-triazol-3-yl)ethyl]amino}carbonyl}}-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-{{[(2-methyl-1,3-thiazol-4-yl)methyl]amino}carbonyl)-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-{{[2-(1H-pyrazol-4-yl)ethyl]amino}carbonyl)-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-4-{{[(1H-indol-6-ylmethyl)amino]carbonyl}-5-{{[(4-methoxyphenyl)amino]methyl}-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-{{[(2-methylimidazo[2,1-b][1,3]thiazol-6-yl)methyl]amino}carbonyl)-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-{{[(5-methyl-4H-1,2,4-triazol-3-yl)methyl]amino}carbonyl)-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-{{[(1-methyl-1H-pyrazol-4-yl)methyl]amino}carbonyl)-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-{{[(1-methyl-5-oxopyrrolidin-2-yl)methyl]amino}carbonyl)-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-4-{{[2-(6-methoxy-1H-benzimidazol-2-yl)ethyl]amino}carbonyl)-5-{{[(4-methoxyphenyl)amino]methyl}-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-{{[2-(1H-1,2,4-triazol-5-yl)ethyl]amino}carbonyl)-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-{{[(1-methyl-1H-imidazol-2-yl)methyl]amino}carbonyl)-1H-pyrrole-2-carboxylate;

tert-butyl 4-{{[(2,3-dihydroimidazo[2,1-b][1,3]thiazol-6-ylmethyl)amino]carbonyl}-3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-{{[(4-methyl-1H-imidazol-2-yl)methyl]amino}carbonyl)-1H-pyrrole-2-carboxylate

tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-{{[(8-methylimidazo[1,2-a]pyridin-2-yl)methyl]amino}carbonyl)-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-{{[1-(5-methyl-4H-1,2,4-triazol-3-yl)ethyl]amino}carbonyl)-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-{{[(quinolin-2-ylmethyl)amino]carbonyl)-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-[[[4-methoxyphenyl]amino]methyl]-4-([[(6-methylpyridin-2-yl)methyl]amino]carbonyl)-1H-pyrrole-2-carboxylate;

Tert-butyl 3-ethyl-5-[[[4-methoxyphenyl]amino]methyl]-4-([[(4-methyl-1,3-thiazol-2-yl)methyl]amino]carbonyl)-1H-pyrrole-2-carboxylate;

Tert-butyl 4-([[(6,7-dihydro-5H-cyclopenta[b]pyridin-3-ylmethyl)amino]carbonyl]-3-ethyl-5-[[[4-methoxyphenyl]amino]methyl]-1H-pyrrole-2-carboxylate;

Tert-butyl 3-ethyl-5-[[[4-methoxyphenyl]amino]methyl]-4-([[(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-3-ylmethyl)amino]carbonyl]-1H-pyrrole-2-carboxylate;

Tert-butyl 3-ethyl-5-[[[4-methoxyphenyl]amino]methyl]-4-([[(2-(4-methyl-1,3-thiazol-5-yl)ethyl)amino]carbonyl)-1H-pyrrole-2-carboxylate;

Tert-butyl 3-ethyl-5-[[[4-methoxyphenyl]amino]methyl]-4-([[(1-methylpiperidin-3-yl)methyl]amino]carbonyl)-1H-pyrrole-2-carboxylate;

Tert-butyl 3-ethyl-5-[[[4-methoxyphenyl]amino]methyl]-4-([[(2-morpholin-4-yl-2-pyridin-4-ylethyl)amino]carbonyl]-1H-pyrrole-2-carboxylate;

Tert-butyl 3-ethyl-5-[[[4-methoxyphenyl]amino]methyl]-4-([[(2-morpholin-4-yl-2-pyridin-3-ylethyl)amino]carbonyl)-1H-pyrrole-2-carboxylate;

Tert-butyl 3-ethyl-4-([[(5-fluoro-2-oxo-2,3-dihydro-1H-indol-3-yl)methyl]amino]carbonyl)-5-[[[4-methoxyphenyl]amino]methyl]-1H-pyrrole-2-carboxylate;

Tert-butyl 4-([[(5-cyclopropyl-1H-pyrazol-3-yl)methyl]amino]carbonyl)-3-ethyl-5-[[[4-methoxyphenyl]amino]methyl]-1H-pyrrole-2-carboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-[[[hydroxy(pyridin-2-ylmethyl)amino]methyl]-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-(pyridin-2-ylmethyl) 3-ethyl-5-[[[4-methoxyphenyl]amino]methyl]-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-[[[4-chlorophenyl]amino]methyl]-3-(2-phenylethyl)-1H-pyrrole-2,4-dicarboxylate;

2-amino-N-[[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl]glycinamide;

4-(Carbamoylmethyl-carbamoyl)-3-ethyl-5-[[[4-methoxy-phenylamino]-methyl]-1H-pyrrole-2-carboxylic acid tert-butyl ester;

or a pharmaceutically acceptable salt or stereoisomer thereof.

Also included in the instant invention is a TFA salt of a compound selected from:

- 5 2-tert-Butyl 4-methyl 3-ethyl-5-{[(3-fluoro-4-methoxyphenyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-{[(2-methyl-1,3-benzothiazol-6-yl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[4-(1H-pyrazol-1-yl)phenyl]amino} methyl)-1H-pyrrole-2,4-dicarboxylate;
- 10 2-tert-butyl 4-methyl 3-ethyl-5-({[4-(2-oxoimidazolidin-1-yl)phenyl]amino} methyl)-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[4-(3-methyl-2-oxoimidazolidin-1-yl)phenyl]amino} methyl)-1H-pyrrole-2,4-dicarboxylate;
- 15 2-tert-butyl 4-methyl 3-ethyl-5-{[(3-fluoro-4-methoxyphenyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-{[(cyclopropylmethyl)amino]methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-{[(4-phenoxyphenyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate;
- 20 2-tert-butyl 4-methyl 5-({[4-(aminocarbonyl) phenyl]amino} methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 4-({[5-(tert-butoxycarbonyl)-4-ethyl-3-(methoxycarbonyl)-1H-pyrrol-2-yl]methyl} amino)-2-hydroxybenzoic acid;
- 25 2-tert-butyl 4-methyl 5-[(cyclopropylamino)methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-{[(6-chloro-1,3-benzothiazol-2-yl)amino] methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-{[(2-chloropyrimidin-4-yl)amino]methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 30 2,4-dicarboxylate;

- 2-tert-butyl 4-methyl 5-{[(2-chloro-6,7-dimethoxyquinazolin-4-yl)amino]methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-{[(5-bromopyridin-2-yl)amino]methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 5 2-tert-butyl 4-methyl 3-ethyl-5-[(pyrimidin-2-ylamino)methyl]-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-[(1,3-benzoxazol-2-ylamino)methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-{[(5-bromopyrimidin-2-yl)amino]methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 10 2-tert-butyl 4-methyl 5-({[5-chloro-2-(4H-1,2,4-triazol-4-yl)benzyl] amino}methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[3-hydroxy-5-(hydroxymethyl)-2-methylpyridin-4-yl]methyl}amino)methyl)-1H-pyrrole-2,4-dicarboxylate;
- 15 2-tert-butyl 4-methyl 5-({[2-(3,4-dihydroxyphenyl)-2-hydroxyethyl]amino}methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-({[2-(aminocarbonyl) cyclohexyl]amino}methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-{[(5-bromo-2-fluorobenzyl)amino]methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 20 2-tert-butyl 4-methyl 5-({[2-(3,4-dichlorophenyl) ethyl]amino}methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[2-(1H-1,2,4-triazol-1-yl)ethyl] amino}methyl)-1H-pyrrole-2,4-dicarboxylate;
- 25 2-tert-butyl 4-methyl 5-({[4-(4-tert-butoxyphenyl)butyl]amino}methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-({[1-(1H-benzimidazol-2-yl)ethyl]amino}methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[2-(1H-1,2,4-triazol-3-yl)ethyl] amino}methyl)-1H-pyrrole-2,4-dicarboxylate;
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- 2-tert-butyl 4-methyl 3-ethyl-5-({[2-(4-methyl-1,3-thiazol-5-yl)ethyl] amino}methyl)-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[(1-morpholin-4-ylcyclopentyl)methyl] amino}methyl)-1H-pyrrole-2,4-dicarboxylate;
- 5 2-tert-butyl 4-methyl 3-ethyl-5-({[(2-piperidin-1-yl-2-pyridin-3-ylethyl) amino]methyl}-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[(3-phenylisoxazol-5-yl)methyl]amino}methyl)-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[(2-morpholin-4-yl-2-pyridin-2-ylethyl) amino] methyl}-1H-pyrrole-2,4-dicarboxylate;
- 10 2-tert-butyl 4-methyl 3-ethyl-5-({[(1-morpholin-4-ylcycloheptyl)methyl] amino} methyl)-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[(2,2,2-trifluoro-1-pyridin-3-ylethyl) amino]methyl}-1H-pyrrole-2,4-dicarboxylate;
- 15 2-tert-butyl 4-methyl 3-ethyl-5-({[(2-thien-2-yl-1,3-thiazol-4-yl)methyl] amino} methyl)-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[2-(5-phenyl-1H-1,2,4-triazol-3-yl) ethyl] amino}methyl)-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[(6-methoxy-1H-benzimidazol-2-yl)methyl] amino}methyl)-1H-pyrrole-2,4-dicarboxylate;
- 20 2-tert-butyl 4-methyl 5-({[(2,3-dihydro-1,4-benzodioxin-2-ylmethyl) amino]methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({methyl[(5-phenylisoxazol-3-yl) methyl]amino} methyl)-1H-pyrrole-2,4-dicarboxylate;
- 25 2-tert-butyl 4-methyl 3-ethyl-5-[(quinoxalin-2-ylamino)methyl]-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-({[(1,2-diphenylethyl) amino]methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-({[(2,2-diphenylethyl) amino]methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 30 dicarboxylate;

- 2-tert-butyl 4-methyl 5-[(2-[4-(aminosulfonyl) phenyl]ethyl)amino]methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-[(3,4-dihydroxybenzyl) amino]methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 5 2-tert-butyl 4-methyl 5-[(1-benzylpiperidin-4-yl)amino]methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-[(4-(aminosulfonyl) benzyl)amino]methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-[(2-morpholin-4-yl-2-pyridin-3-ylethyl) amino]methyl]-1H-pyrrole-2,4-dicarboxylate;
- 10 2-tert-butyl 4-methyl 5-[(1-(tert-butoxycarbonyl)-1H-indol-3-yl)methyl] amino]methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-[(4-benzylmorpholin-3-yl)methyl]amino]methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 15 2-tert-butyl 4-methyl 3-ethyl-5-[(4-phenylmorpholin-3-yl) methyl]amino]methyl)-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-[(methyl[(5-methyl-1H-indol-3-yl) methyl]amino]methyl)-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-[(1,3-benzothiazol-2-ylamino)methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 20 2-tert-butyl 4-methyl 3-ethyl-5-[(1-phenyl-1H-tetrazol-5-yl)amino] methyl)-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-[(2R)-2-(3-fluorophenyl)-2-hydroxyethyl]amino]methyl)-1H-pyrrole-2,4-dicarboxylate;
- 25 2-tert-butyl 4-methyl 3-ethyl-5-[(2R)-2-(3-fluorophenyl)-2-hydroxyethyl][(2S)-2-(3-fluorophenyl)-2-hydroxyethyl]amino] methyl)-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-[(2R)-2-(4-fluorophenyl)-2-hydroxyethyl]amino]methyl)-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-[(bis[(2R)-2-(4-fluorophenyl)-2-hydroxyethyl]amino]methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 30

- 2-tert-butyl 4-methyl 3-ethyl-5-({[(2S)-2-(4-fluorophenyl)-2-hydroxyethyl]amino} methyl)-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[1-(4-fluorophenyl)-2-hydroxyethyl]amino} methyl)-1H-pyrrole-2,4-dicarboxylate;
- 5 2-tert-butyl 4-methyl 5-({bis[(2S)-2-(4-fluorophenyl)-2-hydroxyethyl]amino}methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[(2S)-2-(4-fluorophenyl)-2-hydroxyethyl][1-(4-fluorophenyl)-2-hydroxyethyl]amino} methyl)-1H-pyrrole-2,4-dicarboxylate;
- 10 or a stereoisomer thereof.

Additional examples of compounds of the instant invention include:

- 2-tert-Butyl 4-methyl 3-ethyl-5-({[(3-fluoro-4-methoxyphenyl)amino]methyl})-1H-pyrrole-2,4-dicarboxylate;
- 15 2-tert-butyl 4-methyl 3-ethyl-5-({[(2-methyl-1,3-benzothiazol-6-yl)amino]methyl})-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[4-(1H-pyrazol-1-yl)phenyl]amino} methyl)-1H-pyrrole-2,4-dicarboxylate;
- 20 2-tert-butyl 4-methyl 3-ethyl-5-({[4-(2-oxoimidazolidin-1-yl)phenyl]amino}methyl)-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[4-(3-methyl-2-oxoimidazolidin-1-yl)phenyl]amino}methyl)-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[(3-fluoro-4-methoxyphenyl)amino]methyl})-1H-pyrrole-2,4-dicarboxylate;
- 25 2-tert-butyl 4-methyl 5-({[(cyclopropylmethyl)amino]methyl})-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[(4-phenoxyphenyl)amino]methyl})-1H-pyrrole-2,4-dicarboxylate;

- 2-tert-butyl 4-methyl 5-([4-(aminocarbonyl) phenyl]amino)methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 4-([5-(tert-butoxycarbonyl)-4-ethyl-3-(methoxycarbonyl)-1H-pyrrol-2-yl]methyl)amino)-2-hydroxybenzoic acid;
- 5 2-tert-butyl 4-methyl 5-[(cyclopropylamino)methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-[(6-chloro-1,3-benzothiazol-2-yl)amino]methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-[(2-chloropyrimidin-4-yl)amino]methyl)-3-ethyl-1H-pyrrole-
- 10 2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-[(2-chloro-6,7-dimethoxyquinazolin-4-yl)amino]methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-[(5-bromopyridin-2-yl)amino]methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 15 2-tert-butyl 4-methyl 3-ethyl-5-[(pyrimidin-2-ylamino)methyl]-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-[(1,3-benzoxazol-2-ylamino)methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-[(5-bromopyrimidin-2-yl)amino]methyl)-3-ethyl-1H-pyrrole-
- 20 2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-([5-chloro-2-(4H-1,2,4-triazol-4-yl)benzyl] amino)methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-([3-hydroxy-5-(hydroxymethyl)-2-methylpyridin-4-yl]methyl)amino)methyl)-1H-pyrrole-2,4-dicarboxylate;
- 25 2-tert-butyl 4-methyl 5-([2-(3,4-dihydroxyphenyl)-2-hydroxyethyl]amino)methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-([2-(aminocarbonyl) cyclohexyl]amino)methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-[(5-bromo-2-fluorobenzyl)amino]methyl)-3-ethyl-1H-
- 30 pyrrole-2,4-dicarboxylate;

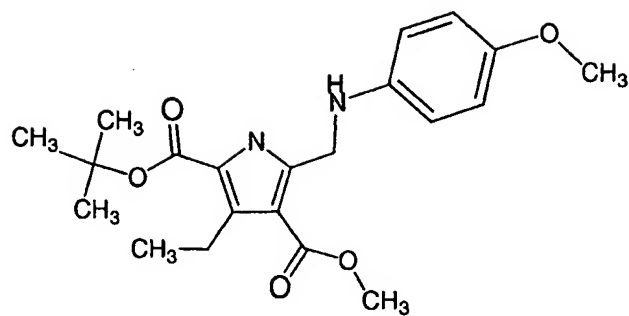
- 2-tert-butyl 4-methyl 5-({[2-(3,4-dichlorophenyl) ethyl]amino}methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[2-(1H-1,2,4-triazol-1-yl)ethyl] amino}methyl)-1H-pyrrole-2,4-dicarboxylate;
- 5 2-tert-butyl 4-methyl 5-({[4-(4-tert-butoxyphenyl)butyl]amino}methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-({[1-(1H-benzimidazol-2-yl)ethyl]amino}methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[2-(1H-1,2,4-triazol-3-yl)ethyl] amino}methyl)-1H-pyrrole-2,4-dicarboxylate;
- 10 2-tert-butyl 4-methyl 3-ethyl-5-({[2-(4-methyl-1,3-thiazol-5-yl)ethyl] amino}methyl)-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[(1-morpholin-4-ylcyclopentyl)methyl] amino}methyl)-1H-pyrrole-2,4-dicarboxylate;
- 15 2-tert-butyl 4-methyl 3-ethyl-5-({[(2-piperidin-1-yl-2-pyridin-3-ylethyl) amino]methyl}-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[(3-phenylisoxazol-5-yl)methyl]amino}methyl)-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[(2-morpholin-4-yl-2-pyridin-2-ylethyl) amino] methyl}-1H-pyrrole-2,4-dicarboxylate;
- 20 2-tert-butyl 4-methyl 3-ethyl-5-({[(1-morpholin-4-ylcycloheptyl)methyl] amino} methyl)-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[(2,2,2-trifluoro-1-pyridin-3-ylethyl) amino]methyl}-1H-pyrrole-2,4-dicarboxylate;
- 25 2-tert-butyl 4-methyl 3-ethyl-5-({[(2-thien-2-yl-1,3-thiazol-4-yl)methyl] amino} methyl)-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[2-(5-phenyl-1H-1,2,4-triazol-3-yl) ethyl] amino}methyl)-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[(6-methoxy-1H-benzimidazol-2-yl)methyl] amino}methyl)-1H-pyrrole-2,4-dicarboxylate;
- 30

- 2-tert-butyl 4-methyl 5-{[(2,3-dihydro-1,4-benzodioxin-2-ylmethyl) amino]methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({methyl[(5-phenylisoxazol-3-yl) methyl]amino} methyl)-1H-pyrrole-2,4-dicarboxylate;
- 5 2-tert-butyl 4-methyl 3-ethyl-5-[(quinoxalin-2-ylamino)methyl]-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-{[(1,2-diphenylethyl) amino]methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-{[(2,2-diphenylethyl) amino]methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 10 2-tert-butyl 4-methyl 5-[(2-[4-(aminosulfonyl) phenyl]ethyl)amino] methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-{[(3,4-dihydroxybenzyl) amino]methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 15 2-tert-butyl 4-methyl 5-{[(1-benzylpiperidin-4-yl)amino]methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-({[4-(aminosulfonyl) benzyl]amino} methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-{[(2-morpholin-4-yl-2-pyridin-3-ylethyl) amino] methyl}-1H-pyrrole-2,4-dicarboxylate;
- 20 2-tert-butyl 4-methyl 5-[(1-(tert-butoxycarbonyl)-1H-indol-3-yl)methyl] amino) methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-({[(4-benzylmorpholin-3-yl)methyl]amino} methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 25 2-tert-butyl 4-methyl 3-ethyl-5-({[(4-phenylmorpholin-3-yl) methyl]amino} methyl)-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({methyl[(5-methyl-1H-indol-3-yl) methyl]amino} methyl)-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-[(1,3-benzothiazol-2-ylamino)methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 30 dicarboxylate;

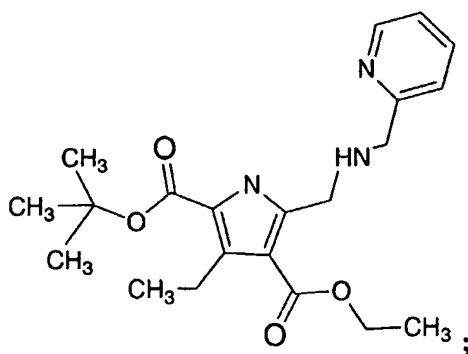
- 2-tert-butyl 4-methyl 3-ethyl-5-{{[(1-phenyl-1H-tetrazol-5-yl)amino] methyl}-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-{{[(2R)-2-(3-fluorophenyl)-2-hydroxyethyl]amino} methyl}-1H-pyrrole-2,4-dicarboxylate;
- 5 2-tert-butyl 4-methyl 3-ethyl-5-{{[(2R)-2-(3-fluorophenyl)-2-hydroxyethyl][(2S)-2-(3-fluorophenyl)-2-hydroxyethyl]amino} methyl}-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-{{[(2R)-2-(4-fluorophenyl)-2-hydroxyethyl]amino} methyl}-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-{{bis[(2R)-2-(4-fluorophenyl)-2-hydroxyethyl]amino} methyl)-10 3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-{{[(2S)-2-(4-fluorophenyl)-2-hydroxyethyl]amino} methyl}-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-{{[1-(4-fluorophenyl)-2-hydroxyethyl]amino} methyl}-1H-pyrrole-2,4-dicarboxylate;
- 15 2-tert-butyl 4-methyl 5-{{bis[(2S)-2-(4-fluorophenyl)-2-hydroxyethyl]amino} methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-{{[(2S)-2-(4-fluorophenyl)-2-hydroxyethyl][1-(4-fluorophenyl)-2-hydroxyethyl]amino} methyl}-1H-pyrrole-2,4-dicarboxylate;
- 20 or a pharmaceutically acceptable salt or stereoisomer thereof.

Specific examples of compounds of the instant invention include

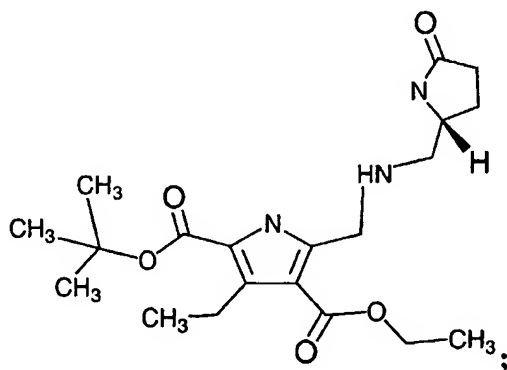
- 2-tert-butyl 4-methyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-1H-pyrrole-2,4-25 dicarboxylate



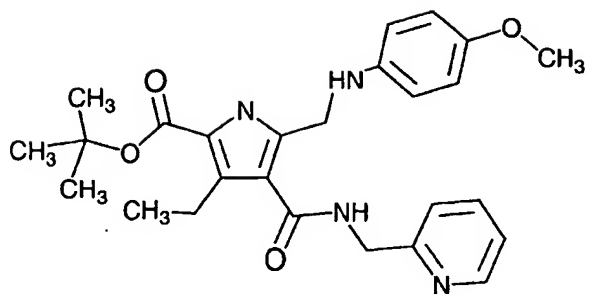
2-tert-butyl 4-ethyl 3-ethyl-5-[[[(pyridin-2-ylmethyl)amino]methyl]-1H-pyrrole-2,4-dicarboxylate



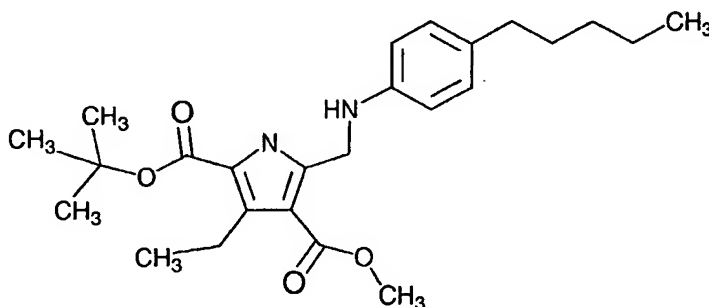
5 2-tert-butyl 4-ethyl 3-ethyl-5-[[[[(2R)-5-oxopyrrolidin-2-yl]methyl]amino]methyl]-1H-pyrrole-2,4-dicarboxylate



tert-butyl 3-ethyl-5-[[[(4-methoxyphenyl)amino]methyl]-4-[[[(pyridin-2-ylmethyl)amino]carbonyl]-1H-pyrrole-2-carboxylate



2-tert-butyl 4-methyl 3-ethyl-5-([(4-pentylphenyl)amino]methyl)-1H-pyrrole-2,4-dicarboxylate



5 or the pharmaceutically acceptable salt or stereoisomer thereof.

The compounds of the present invention may have asymmetric centers, chiral axes, and chiral planes (as described in: E.L. Eliel and S.H. Wilen, *Stereochemistry of Carbon Compounds*, John Wiley & Sons, New York, 1994, pages 1119-1190), and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers and mixtures thereof, including optical isomers, being included in the present invention. In addition, the compounds disclosed herein may exist as tautomers and both tautomeric forms are intended to be encompassed by the scope of the invention, even though only one tautomeric structure is depicted.

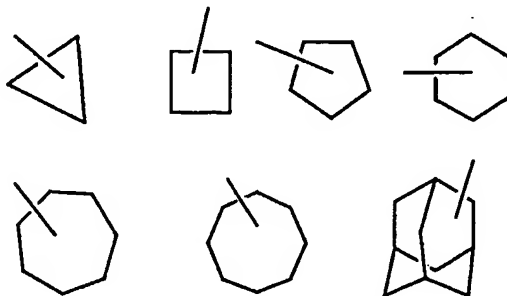
When any variable (e.g. aryl, heterocycle, R¹, R^a etc.) occurs more than one time in any constituent, its definition on each occurrence is independent at every other occurrence. Also, combinations of substituents and variables are permissible only if such combinations result in stable compounds.

Lines drawn into the ring systems from substituents indicate that the indicated bond may be attached to any of the substitutable ring carbon atoms or heteroatoms.

It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials.

As used herein, "alkyl" is intended to include both branched, straight-chain, and cyclic saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, C₁-C₁₀, as in "C₁-C₁₀ alkyl" is defined to include groups having 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbons in a linear or branched arrangement. For example, "C₁-C₁₀ alkyl" specifically includes methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, adamantyl, and so on.

"Cycloalkyl" as used herein is intended to include non-aromatic cyclic hydrocarbon groups, having the specified number of carbon atoms, which may or may not be bridged or structurally constrained. Examples of such cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl, cyclooctyl, cycloheptyl, tetrahydro-naphthalene, methylenecyclohexyl, and the like. As used herein, examples of "C₃ - C₁₀ cycloalkyl" may include, but are not limited to:



As used herein, the term "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge.

If no number of carbon atoms is specified, the term "alkenyl" refers to a non-aromatic hydrocarbon radical, straight, branched or cyclic, containing from 2 to 10 carbon atoms and at least one carbon to carbon double bond. Preferably one carbon to carbon double bond is present, and up to 4 non-aromatic carbon-carbon double bonds may be present. Thus, "C₂-C₆ alkenyl" means an alkenyl radical having from 2 to 6 carbon atoms. Alkenyl groups include ethenyl, propenyl, butenyl and cyclohexenyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkenyl group may contain double bonds and may be substituted if a substituted alkenyl group is indicated.

The term "alkynyl" refers to a hydrocarbon radical straight, branched or cyclic, containing from 2 to 10 carbon atoms and at least one carbon to carbon triple bond. Up to 3 carbon-carbon triple bonds may be present. Thus, "C₂-C₆ alkynyl" means an alkynyl radical having from 2 to 6 carbon atoms. Alkynyl groups include ethynyl, propynyl and butynyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkynyl group may contain triple bonds and may be substituted if a substituted alkynyl group is indicated.

As used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 atoms in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, indanyl, indanonyl, biphenyl, tetralinyl, tetralonyl, fluorenyl, phenanthryl, anthryl, acenaphthyl, tetrahydronaphthyl, and the like.

As appreciated by those of skill in the art, "halo" or "halogen" as used herein is intended to include chloro, fluoro, bromo and iodo.

The term heteroaryl, as used herein, represents a stable monocyclic or bicyclic ring of up to 7 atoms in each ring, wherein at least one ring is aromatic and contains from 1 to 4 heteroatoms selected from the group consisting of O, N and S. Heteroaryl groups within the scope of this definition include but are not limited to: acridinyl, carbazolyl, cinnolinyl, quinoxalinyl, pyrazolyl, indolyl, benzodioxolyl, benzotriazolyl, benzothiofuranyl, benzothiazolyl, furanyl, thienyl, benzothieryl, benzofuranyl, benzoquinolinyl, isoquinolinyl, oxazolyl, isoxazolyl, indolyl, pyrazinyl,

pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, quinolinyl, tetrahydronaphthyl, tetrahydroquinoline, and the like.

- The term heterocycle or heterocyclic or heterocyclyl, as used herein, represents a stable 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure.
- 5 “Heterocycle” or “heterocyclyl” therefore includes the above mentioned heteroaryls, as well as dihydro and tetrathydro analogs thereof. Further examples of “heterocyclyl” include, but are not limited to the following: benzodioxolyl, benzodioxinyl, benzofuranyl, benzofurazanyl, benzoimidazolyl, benzopyranyl, benzopyrazolyl, benzotriazolyl, benzothiazolyl, benzothienyl, benzothiofuranyl, benzothiophenyl, benzothiopyranyl, benzoxazolyl, carbazolyl, carbolinyl, chromanyl, cinnolinyl, diazapinonyl, dihydrobenzofuranyl, dihydrobenzofuryl, dihydrobenzoimidazolyl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrocyclopentapyridinyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidyl, furyl, furanyl, imidazolyl, imidazoliny, imidazolidinyl, imidazothiazolyl, imidazopyridinyl, indazolyl, indolazinyl, indolinyl, indolyl, isobenzofuranyl, isochromanyl, isoindolyl, isoindolinyl, isoquinolinone, isoquinolyl, isothiazolyl, isothiazolidinyl, isoxazoliny, isoxazolyl, methylenedioxybenzoyl, morpholinyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazoliny, oxetanyl, oxoazepinyl, oxadiazolyl, oxodihydrophthalazinyl, oxodihydroindolyl, oxoimidazolidinyl, oxopiperazinyl, oxopiperdinyl, oxopyrrolidinyl, oxopyrimidinyl, oxopyrrolyl, oxotriazolyl, piperidyl, piperidinyl,
- 10
- 15
- 20
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piperazinyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinonyl, pyridopyridinyl,
 pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, pyrrolidinyl, quinazolinyl, quinolinyl,
 quinolyl, quinolinonyl, quinoxalinyl, tetrahydrocycloheptapyridinyl, tetrahydrofuryl,
 tetrahydroisoquinolinyl, tetrahydropyranyl, tetrahydroquinolinyl, tetrazolyl,
 5 tetrazolopyridyl, thiadiazolyl, thiazolyl, thiazolinyl, thienofuryl, thienyl, triazolyl,
 azetidiny, 1,4-dioxanyl, hexahydroazepinyl, and the like. Preferably, heterocycle is
 selected from oxoazepinyl, benzimidazolyl, diazapinonyl, imidazolyl,
 oxoimidazolidinyl, indolyl, isoquinolinyl, morpholinyl, piperidyl, piperazinyl,
 pyridyl, pyrrolidinyl, oxopiperidinyl, oxopyrimidinyl, oxopyrrolidinyl, quinolinyl,
 10 tetrahydrofuryl, tetrahydroisoquinolinyl, and thienyl.

As used herein, "aralkyl" is intended to mean an aryl moiety, as
 defined above, attached through a C₁-C₁₀ alkyl linker, where alkyl is defined above.
 Examples of aralkyls include, but are not limited to, benzyl, naphthylmethyl and
 phenylpropyl.

15 As used herein, "heterocyclalkyl" is intended to mean a heterocyclic
 moiety, as defined below, attached through a C₁-C₁₀ alkyl linker, where alkyl is
 defined above. Examples of heterocyclalkyls include, but are not limited to,
 pyridylmethyl, imidazolylethyl, pyrrolidinylmethyl, morpholinylethyl,
 quinolinylmethyl, imidazolylpropyl and the like.

20 As used herein, the terms "substituted C₁-C₁₀ alkyl" and "substituted
 C₁-C₆ alkoxy" are intended to include the branch or straight-chain alkyl group of the
 specified number of carbon atoms, wherein the carbon atoms may be substituted with
 one to three substituents selected from the group which includes, but is not limited to,
 halo, C₁-C₂₀ alkyl, CF₃, NH₂, N(C₁-C₆ alkyl)₂, NO₂, oxo, CN, N₃, -OH, -O(C₁-C₆
 25 alkyl), C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, (C₀-C₆ alkyl) S(O)₀₋₂-,
 (C₀-C₆ alkyl)S(O)₀₋₂(C₀-C₆ alkyl)-, (C₀-C₆ alkyl)C(O)NH-, H₂N-C(NH)-,
 -O(C₁-C₆ alkyl)CF₃, (C₀-C₆ alkyl)C(O)-, (C₀-C₆ alkyl)OC(O)-, (C₀-C₆ alkyl)O
 (C₁-C₆ alkyl)-, (C₀-C₆ alkyl)C(O)₁₋₂(C₀-C₆ alkyl)-, (C₀-C₆ alkyl)OC(O)NH-,

aryl, aralkyl, heterocycle, heterocyclalkyl, halo-aryl, halo-aralkyl, halo-heterocycle, halo-heterocyclalkyl, cyano-aryl, cyano-aralkyl, cyano-heterocycle and cyano-heterocyclalkyl.

As used herein, the terms "substituted C₃-C₁₀ cycloalkyl", "substituted aryl", "substituted heterocycle", "substituted aralkyl" and "substituted heterocyclalkyl" are intended to include the cyclic group containing from 1 to 3 substituents in addition to the point of attachment to the rest of the compound. Preferably, the substituents are selected from the group which includes, but is not limited to, halo, C₁-C₂₀ alkyl, CF₃, NH₂, N(C₁-C₆ alkyl)₂, NO₂, oxo, CN, N₃, -OH, -O(C₁-C₆ alkyl), C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, (C₀-C₆ alkyl) S(O)₀₋₂-, (C₀-C₆ alkyl)S(O)₀₋₂(C₀-C₆ alkyl)-, (C₀-C₆ alkyl)C(O)NH-, H₂N-C(NH)-, -O(C₁-C₆ alkyl)CF₃, (C₀-C₆ alkyl)C(O)-, (C₀-C₆ alkyl)OC(O)-, (C₀-C₆alkyl)O(C₁-C₆ alkyl)-, (C₀-C₆ alkyl)C(O)₁₋₂(C₀-C₆ alkyl)-, (C₀-C₆ alkyl)OC(O)NH-, aryl, aralkyl, heteroaryl, heterocyclalkyl, halo-aryl, halo-aralkyl, halo-heterocycle, halo-heterocyclalkyl, cyano-aryl, cyano-aralkyl, cyano-heterocycle and cyano-heterocyclalkyl.

Preferably, R¹ is selected from H, unsubstituted or substituted C₁-C₁₀ alkyl, halo, OR⁷, N(R⁷)₂, C(O)OR⁷, and -S(O)₂N(R⁵)₂.

Preferably, R² is selected from -C(O)OR⁷, -C(O)N(R⁷)₂, -C(O)NHR⁷OR⁷, -C(O)NH(CR^b₂)_qR⁷, -C(O)NHR⁷NHC(O)R⁷, -C(O)NHR⁷S(O)₂OR⁷, and -C(O)NH(CR^b₂)_qC(O)N(R⁷)₂. More preferably, R² is selected from -C(O)OR⁷, -C(O)N(R⁷)₂, -C(O)NHR⁷OR⁷, -C(O)NH(CR^b₂)_qR⁷.

Preferably, R³ is unsubstituted or substituted C₁-C₁₀ alkyl and unsubstituted or substituted aralkyl.

Preferably, n, p and q are independently 0, 1, 2 or 3. More preferably, n is 1.

It is intended that the definition of any substituent or variable (e.g.,

R¹, R^a, n, etc.) at a particular location in a molecule be independent of its definitions elsewhere in that molecule. Thus, -N(R⁷)₂ represents -NHH, -NHCH₃, -NHC₂H₅, etc. It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide
5 compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials.

For use in medicine, the salts of the compounds of Formula I will be pharmaceutically acceptable salts. Other salts may, however, be useful in the
10 preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. When the compound of the present invention is acidic, suitable "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous,
15 lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins,
20 such as arginine, betaine caffeine, choline, N, N¹-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine,
25 triethylamine, trimethylamine tripropylamine, tromethamine and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric,
30 isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic,

pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric and tartaric acids.

The preparation of the pharmaceutically acceptable salts described
5 above and other typical pharmaceutically acceptable salts is more fully described by Berg et al., "Pharmaceutical Salts," J. Pharm. Sci., 1977:66:1-19.

Included in the instant invention is the free form of compounds of
Formula I, as well as the pharmaceutically acceptable salts and stereoisomers thereof.
Some of the specific compounds exemplified herein are the protonated salts of amine
10 compounds. The term "free form" refers to the amine compounds in non-salt form.
The encompassed pharmaceutically acceptable salts not only include the salts
exemplified for the specific compounds described herein, but also all the typical
pharmaceutically acceptable salts of the free form of compounds of Formula I. The
free form of the specific salt compounds described may be isolated using techniques
15 known in the art. For example, the free form may be regenerated by treating the salt
with a suitable dilute aqueous base solution such as dilute aqueous NaOH, potassium
carbonate, ammonia and sodium bicarbonate. The free forms may differ from their
respective salt forms somewhat in certain physical properties, such as solubility in
polar solvents, but the acid and base salts are otherwise pharmaceutically equivalent
20 to their respective free forms for purposes of the invention.

It will also be noted that the compounds of the present invention
are potentially internal salts or zwitterions, since under physiological conditions
a deprotonated acidic moiety in the compound, such as a carboxyl group, may be
anionic, and this electronic charge might then be balanced off internally against
25 the cationic charge of a protonated or alkylated basic moiety, such as a quaternary
nitrogen atom.

Abbreviations which may be used in the description of the
chemistry and in the Examples that follow include:

30 Ac₂O Acetic anhydride;

	AcOH	Acetic acid;
	AIBN	2,2'-Azobisisobutyronitrile;
	BINAP	2,2'-Bis(diphenylphosphino)-1,1' binaphthyl;
	Bn	Benzyl;
5	BOC/Boc	<i>tert</i> -Butoxycarbonyl;
	BSA	Bovine Serum Albumin;
	CAN	Ceric Ammonia Nitrate;
	CBz	Carbobenzyloxy;
	CI	Chemical Ionization;
10	DBAD	Di- <i>tert</i> -butyl azodicarboxylate;
	DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene;
	DCE	1,2-Dichloroethane;
	DIEA	<i>N,N</i> -Diisopropylethylamine;
	DMAP	4-Dimethylaminopyridine;
15	DME	1,2-Dimethoxyethane;
	DMF	<i>N,N</i> -Dimethylformamide;
	DMSO	Methyl sulfoxide;
	DPPA	Diphenylphosphoryl azide;
	DTT	Dithiothreitol;
20	EDC	1-(3-Dimethylaminopropyl)-3-ethyl-carbodiimide-hydrochloride;
	EDTA	Ethylenediaminetetraacetic acid;
	ES	Electrospray;
	ESI	Electrospray ionization;
	Et ₂ O	Diethyl ether;
25	Et ₃ N	Triethylamine;
	EtOAc	Ethyl acetate;
	EtOH	Ethanol;
	FAB	Fast atom bombardment;
	HEPES	4-(2-Hydroxyethyl)-1-piperazineethanesulfonic acid;
30	HOAc	Acetic acid;

	HOBT	1-Hydroxybenzotriazole hydrate;
	HOObt	3-Hydroxy-1,2,2-benzotriazin-4(3H)-one;
	HPLC	High-performance liquid chromatography;
	HRMS	High Resolution Mass Spectroscopy;
5	KOtBu	Potassium <i>tert</i> -butoxide;
	LAH	Lithium aluminum hydride;
	LCMS	Liquid Chromatography Mass Spectroscopy;
	MCPBA	<i>m</i> -Chloroperoxybenzoic acid;
	Me	Methyl;
10	MeOH	Methanol;
	Ms	Methanesulfonyl;
	MS	Mass Spectroscopy;
	MsCl	Methanesulfonyl chloride;
	<i>n</i> -Bu	<i>n</i> -butyl;
15	<i>n</i> -Bu ₃ P	Tri- <i>n</i> -butylphosphine;
	NaHMDS	Sodium bis(trimethylsilyl)amide;
	NBS	<i>N</i> -Bromosuccinimide;
	Pd(PPh ₃) ₄	Palladium tetrakis(triphenylphosphine);
	Pd ₂ (dba) ₂	Tris(dibenzylideneacetone)dipalladium (0)
20	Ph	phenyl;
	PMSF	α -Toluenesulfonyl fluoride;
	Py or pyr	Pyridine;
	PYBOP (or PyBOP)	Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate;
25	RPLC	Reverse Phase Liquid Chromatography;
	RT	Room Temperature;
	<i>t</i> -Bu	<i>tert</i> -Butyl;
	TBAF	Tetrabutylammonium fluoride;
	TBSCl	<i>tert</i> -Butyldimethylsilyl chloride;
30	TFA	Trifluoroacetic acid;

THF Tetrahydrofuran;
TIPS Triisopropylsilyl;
TMS Tetramethylsilane; and
Tr Trityl.

5

UTILITY

In another aspect, this present invention relates to a method of modulating the catalytic activity of PKs (protein kinases) in a mammal in need thereof comprising contacting the PK with a compound of Formula I.

As used herein, the term “modulation” or “modulating” refers to the alteration of the catalytic activity of receptor tyrosine kinases (RTKs), cellular tyrosine kinases (CTKs) and serine-threonine kinases (STKs). In particular, modulating refers to the activation of the catalytic activity of RTKs, CTKs and STKs, preferably the activation or inhibition of the catalytic activity of RTKs, CTKs and STKs, depending on the concentration of the compound or salt to which the RTKs, CTKs or STKs is exposed or, more preferably, the inhibition of the catalytic activity of RTKs, CTKs and STKs.

The term “catalytic activity” as used herein refers to the rate of phosphorylation of tyrosine under the influence, direct or indirect, of RTKs and/or CTKs or the phosphorylation of serine and threonine under the influence, direct or indirect, of STKs.

The term “contacting” as used herein refers to bringing a compound of this invention and a target PK together in such a manner that the compound can affect the catalytic activity of the PK, either directly; i.e., by interacting with the kinase itself, or indirectly; i.e., by interacting with another molecule on which the catalytic activity of the kinase is dependent. Such “contacting” can be accomplished “*in vitro*,” i.e., in a test tube, a petri dish or the like. In a test tube, contacting may involve only a compound and a PK of interest or it may involve whole cells. Cells may also be maintained or grown in cell culture dishes and contacted with a compound in that

environment. In this context, the ability of a particular compound to affect a PK related disorder; i.e., the IC₅₀ of the compound, defined below, can be determined before use of the compounds *in vivo* with more complex living organisms is attempted. For cells outside the organism, multiple methods exist, and are well known to those skilled in the art, to get the PKs in contact with the compounds including, but not limited to, direct cell microinjection and numerous transmembrane carrier techniques.

The above-referenced PK is selected from the group comprising an RTK, a CTK or an STK in another aspect of this invention. Preferably, the PK is an RTK.

Furthermore, it is an aspect of this invention that the receptor tyrosine kinase (RTK) whose catalytic activity is modulated by a compound of this invention is selected from the group comprising EGF, HER2, HER3, HER4, IR, IGF-1R, IRR, PDGFR α , PDGFR β , TrkA, TrkB, TrkC, HGF, CSFIR, C-Kit, C-fms, Flk-1R, Flk4, KDR/Flk-1, Flt-1, FGFR-1R, FGFR-1R, FGFR-3R and FGFR-4R. Preferably, the RTK is preferably, the receptor protein kinase is selected from IR, IGF-1R, or IRR.

In addition, it is an aspect of this invention that the cellular tyrosine kinase whose catalytic activity is modulated by a compound of this invention is selected from the group consisting of Src, Frk, Btk, Csk, Abl, ZAP70, Fes, Fps, Fak, Jak, Ack, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr and Yrk.

Another aspect of this invention is that the serine-threonine protein kinase whose catalytic activity is modulated by a compound of this invention is selected from the group consisting of CDK2 and Raf.

In another aspect, this invention relates to a method for treating or preventing a PK-related disorder in a mammal in need of such treatment comprising administering to the mammal a therapeutically effective amount of one or more of the compounds described above.

As used herein, "PK-related disorder," "PK driven disorder," and "abnormal PK activity" all refer to a condition characterized by inappropriate (i.e., diminished or, more commonly, excessive) PK catalytic activity, where the particular

PK can be an RTK, a CTK or an STK. Inappropriate catalytic activity can arise as the result of either: (1) PK expression in cells which normally do not express PKs; (2) increased PK expression leading to unwanted cell proliferation, differentiation and/or growth; or, (3) decreased PK expression leading to unwanted reductions in cell proliferation, differentiation and/or growth. Excessive-activity of a PK refers to either amplification of the gene encoding a particular PK or its ligand, or production of a level of PK activity which can correlate with a cell proliferation, differentiation and/or growth disorder (that is, as the level of the PK increases, the severity of one or more symptoms of a cellular disorder increase as the level of the PK activity decreases).

10 “Treat,” “treating” or “treatment” with regard to a PK-related disorder refers to alleviating or abrogating the cause and/or the effects of a PK-related disorder.

As used herein, the terms “prevent”, “preventing” and “prevention” refer to a method for barring a mammal from acquiring a PK-related disorder in the first place.

15 The term “administration” and variants thereof (e.g., “administering” a compound) in reference to a compound of the invention means introducing the compound or a prodrug of the compound into the system of the animal in need of treatment. When a compound of the invention or prodrug thereof is provided in combination with one or more other active agents (e.g., a cytotoxic agent, etc.), “administration” and its variants are each understood to include concurrent and sequential introduction of the compound or prodrug thereof and other agents.

25 The term “therapeutically effective amount” as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

30 The term “treating cancer” or “treatment of cancer” refers to administration to a mammal afflicted with a cancerous condition and refers to an effect that alleviates the cancerous condition by killing the cancerous cells, but also to an effect that results in the inhibition of growth and/or metastasis of the cancer.

The protein kinase-related disorder may be selected from the group comprising an RTK, a CTK or an STK-related disorder in a further aspect of this invention. Preferably, the protein kinase-related disorder is an RTK-related disorder.

In yet another aspect of this invention, the above referenced PK-related
5 disorder may be selected from the group consisting of an EGFR-related disorder, a PDGFR-related disorder, an IGFR-related disorder and a flk-related disorder.

The above referenced PK-related disorder may be a cancer selected from, but not limited to, astrocytoma, basal or squamous cell carcinoma, brain cancer, glioblastoma, bladder cancer, breast cancer, colorectal cancer, chondrosarcoma,
10 cervical cancer, adrenal cancer, choriocarcinoma, esophageal cancer, endometrial carcinoma, erythroleukemia, Ewing's sarcoma, gastrointestinal cancer, head and neck cancer, hepatoma, glioma, hepatocellular carcinoma, leukemia, leiomyoma, melanoma, non-small cell lung cancer, neural cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cell carcinoma, rhabdomyosarcoma, small cell lung
15 cancer, thymoma, thyroid cancer, testicular cancer and osteosarcoma in a further aspect of this invention. More preferably, the PK-related disorder is a cancer selected from brain cancer, breast cancer, prostate cancer, colorectal cancer, small cell lung cancer, non-small cell lung cancer, renal cell carcinoma or endometrial carcinoma.

Included within the scope of the present invention is a pharmaceutical
20 composition, which is comprised of a compound of Formula I as described above and a pharmaceutically acceptable carrier. The present invention also encompasses a method of treating or preventing cancer in a mammal in need of such treatment which is comprised of administering to said mammal a therapeutically effective amount of a compound of Formula I. Types of cancers which may be treated using compounds of
25 Formula I include, but are not limited to, astrocytoma, basal or squamous cell carcinoma, brain cancer, glioblastoma, bladder cancer, breast cancer, colorectal cancer, chondrosarcoma, cervical cancer, adrenal cancer, choriocarcinoma, esophageal cancer, endometrial carcinoma, erythroleukemia, Ewing's sarcoma, gastrointestinal cancer, head and neck cancer, hepatoma, glioma, hepatocellular carcinoma, leukemia,
30 leiomyoma, melanoma, non-small cell lung cancer, neural cancer, ovarian cancer,

pancreatic cancer, prostate cancer, renal cell carcinoma, rhabdomyosarcoma, small cell lung cancer, thymoma, thyroid cancer, testicular cancer and osteosarcoma in a further aspect of this invention. More preferably, the cancer being treated is selected from breast cancer, prostate cancer, colorectal cancer, small cell lung cancer, non-
5 small cell lung cancer, renal cell carcinoma, or endometrial carcinoma.

The above-referenced PK-related disorder may be an IGFR-related disorder selected from diabetes, an autoimmune disorder, Alzheimer's and other cognitive disorders, a hyperproliferation disorder, aging, cancer, acromegaly, Crohn's disease, endometriosis, diabetic retinopathy, restenosis, fibrosis, psoriasis,
10 osteoarthritis, rheumatoid arthritis, an inflammatory disorder and angiogenesis in yet another aspect of this invention.

A method of treating or preventing retinal vascularization which is comprised of administering to a mammal in need of such treatment a therapeutically effective amount of compound of Formula I is also encompassed by the present
15 invention. Methods of treating or preventing ocular diseases, such as diabetic retinopathy and age-related macular degeneration, are also part of the invention. Also included within the scope of the present invention is a method of treating or preventing inflammatory diseases, such as rheumatoid arthritis, psoriasis, contact dermatitis and delayed hypersensitivity reactions, as well as treatment or prevention
20 of bone associated pathologies selected from osteosarcoma, osteoarthritis, and rickets.

Other disorders which might be treated with compounds of this invention include, without limitation, immunological and cardiovascular disorders such as atherosclerosis.

The invention also contemplates the use of the instantly claimed
25 compounds in combination with a second compound selected from the group consisting of:

- 1) an estrogen receptor modulator,
- 2) an androgen receptor modulator,
- 3) retinoid receptor modulator,
- 30 4) a cytotoxic agent,

- 5) an antiproliferative agent,
6) a prenyl-protein transferase inhibitor,
7) an HMG-CoA reductase inhibitor,
8) an HIV protease inhibitor,
5 9) a reverse transcriptase inhibitor, and
10) angiogenesis inhibitor.

A preferred angiogenesis inhibitor is selected from the group consisting of a tyrosine kinase inhibitor, an inhibitor of epidermal-derived growth factor, an inhibitor of fibroblast-derived growth factor, an inhibitor of platelet derived
10 growth factor, an MMP inhibitor, an integrin blocker, interferon- α , interleukin-12, pentosan polysulfate, a cyclooxygenase inhibitor, carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin-1, and an antibody to VEGF. Preferred estrogen receptor modulators are tamoxifen and raloxifene.

15 Also included in the scope of the claims is a method of treating cancer, which comprises administering a therapeutically effective amount of a compound of Formula I in combination with a compound selected from the group consisting of:

- 1) an estrogen receptor modulator,
2) an androgen receptor modulator,
20 3) retinoid receptor modulator,
4) a cytotoxic agent,
5) an antiproliferative agent,
6) a prenyl-protein transferase inhibitor,
7) an HMG-CoA reductase inhibitor,
25 8) an HIV protease inhibitor,
9) a reverse transcriptase inhibitor, and
10) angiogenesis inhibitor.

And yet another embodiment is the method of treating cancer using the combination discussed above, in combination with radiation therapy.

And yet another embodiment of the invention is a method of treating cancer which comprises administering a therapeutically effective amount of a compound of Formula I in combination with paclitaxel or trastuzumab.

The PKs whose catalytic activity is modulated by the compounds of this invention
5 include protein tyrosine kinases of which there are two types, receptor tyrosine kinases (RTKs) and cellular tyrosine kinases (CTKs), and serine-threonine kinases (STKs). RTK-mediated signal transduction, is initiated by extracellular interaction with a specific growth factor (ligand), followed by receptor dimerization (or conformational changes in the case of IR, IGF-1R or IRR), transient stimulation of the
10 intrinsic protein tyrosine kinase activity, autophosphorylation and subsequent phosphorylation of other substrate proteins. Binding sites are thereby created for intracellular signal transduction molecules and lead to the formation of complexes with a spectrum of cytoplasmic signaling molecules that facilitate the appropriate cellular response (e.g., cell division, metabolic effects on the extracellular
15 microenvironment, etc.). See Schlessinger and Ullrich, 1992, Neuron 9:303-391.

It has been shown that tyrosine phosphorylation sites, on growth factor receptors, function as high-affinity binding sites for SH2 (src homology) domains of signaling molecules. Fantl et al., 1992, Cell 69:413-423; Songyang et al., 1994, Mol., Cell. Biol. 14:2777-2785; Songyang et al., 1993, Cell 72:767-778; and Koch et al.,
20 1991, Science 252:668-678. Another signaling molecule domain, which interacts with phosphorylated tyrosines, is termed a PTB domain. Blaikie et al., 1994, J. Biol. Chem. 269:32031-32034; Gustafson et al., 1995, Mol. Cell Biol., 15:2500-25008; Kavanaugh and Williams, 1994, Science 266:1862-1865. Several intracellular substrate proteins that associate with RTKs have been identified. They may be
25 divided into two principal groups: (1) substrates which have a catalytic domain; and (2) substrates which lack such domain, but which serve as adapters and associate with catalytically active molecules. Songyang et al., 1993, Cell 72:767-778. The specificity of the interactions between receptors and SH2 domains of their substrates is determined by the amino acid residues immediately surrounding the phosphorylated
30 tyrosine residue. Differences in the binding affinities between SH2 or PTB domains

and the amino acid sequences surrounding the phosphotyrosine residues on particular receptors are consistent with the observed differences in their substrate phosphorylation profiles. Songyang et al., 1993, Cell 72:767-778. These observations suggest that the function of each RTK is determined not only by its
5 pattern of expression and ligand availability, but also by the array of downstream signal transduction pathways that are activated by a particular receptor. Thus, phosphorylation provides an important regulatory step, which determines the selectivity of signaling pathways recruited by specific growth factor receptors, as well as differentiation factor receptors.

10 STKs, being primarily cytosolic, affect the internal biochemistry of the cell, often as a down-stream response to a PTK event. STKs have been implicated in the signaling process which initiates DNA synthesis and subsequent mitosis leading to cell proliferation.

Thus, PK signal transduction results in, among other responses, cell
15 proliferation, differentiation, growth, metabolism, and cellular mobility. Abnormal cell proliferation may result in a wide array of disorders and diseases, including the development of neoplasia such as carcinoma, sarcoma, glioblastoma and hemangioma, disorders such as leukemia, psoriasis, arteriosclerosis, arthritis and diabetic retinopathy and other disorders related to uncontrolled angiogenesis and/or
20 vasculogenesis.

A precise understanding of the mechanism by which the compounds of this invention inhibit PKs is not required in order to practice the present invention. However, while not hereby being bound to any particular mechanism or theory, it is believed that the compounds interact with the amino acids in the catalytic region of
25 PKs. PKs typically possess a bi-lobate structure wherein ATP appears to bind in the cleft between the two lobes in a region where the amino acids are conserved among PKs. Inhibitors of PKs are believed to bind by non-covalent interactions such as hydrogen bonding, van der Waals forces and ionic interactions in the same general region where the aforesaid ATP binds to the PKs. The compounds disclosed herein

may have utility as *in vitro* assays for such proteins as well as exhibiting *in vivo* therapeutic effects through interaction with such proteins.

In another aspect, the protein kinase (PK), the catalytic activity of which is modulated by contact with a compound of this invention, is a protein
5 tyrosine kinase (PTK), more particularly, a receptor protein tyrosine kinase (RTK). Among the RTKs whose catalytic activity can be modulated with a compound of this invention, or salt thereof, are, without limitation, EGF, HER2, HER3, HER4, IR, IGF-1R, IRR, PDGFR α , PDGFR β , TrkA, TrkB, TrkC, HGF, CSFIR, C-Kit, C-fms, Flk-1R, Flk4, KDR/Flk-1, Flt-1, FGFR-1R, FGFR-2R, FGFR-3R and FGFR-4R.
10 Most preferably, the RTK is selected from IGF-1R.

The protein tyrosine kinase whose catalytic activity is modulated by contact with a compound of this invention, or a salt or a prodrug thereof, can also be a non-receptor or cellular protein tyrosine kinase (CTK). Thus, the catalytic activity of CTKs such as, without limitation, Src, Frk, Btk, Csk, Abl, ZAP70, Fes, Fps, Fak, Jak,
15 Ack, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr and Yrk, may be modulated by contact with a compound or salt of this invention.

Still another group of PKs which may have their catalytic activity modulated by contact with a compound of this invention are the serine-threonine protein kinases such as, without limitation, CDK2 and Raf.

20 This invention is also directed to compounds that modulate PK signal transduction by affecting the enzymatic activity of RTKs, CTKs and/or STKs, thereby interfering with the signals transduced by such proteins. More particularly, the present invention is directed to compounds which modulate RTK, CTK and/or STK mediated signal transduction pathways as a therapeutic approach to cure many kinds
25 of solid tumors, including, but not limited to, carcinomas, sarcomas including Kaposi's sarcoma, erythroblastoma, glioblastoma, meningioma, astrocytoma, melanoma and myoblastoma. Treatment or prevention of non-solid tumor cancers such as leukemia are also contemplated by this invention. Indications may include, but are not limited to brain cancers, bladder cancers, ovarian cancers, gastric cancers,

pancreatic cancers, colon cancers, blood cancers, breast cancers, prostate cancers, renal cell carcinomas, lung cancer and bone cancers.

Further examples, without limitation, of the types of disorders related to inappropriate PK activity that the compounds described herein may be useful in preventing, treating and studying, are cell proliferative disorders, fibrotic disorders and metabolic disorders.

As previously mentioned, the Insulin-like Growth Factor-1 Receptor (IGF-1R) belongs to the family of transmembrane tyrosine kinase receptors such as platelet-derived growth factor receptor, the epidermal growth factor receptor, and the insulin receptor. There are two known ligands for the IGF-1R receptor. They are IGF-1 and IGF-2. As used herein, the term "IGF" refers to both IGF-1 and IGF-2. The insulin-like growth factor family of ligands, receptors and binding proteins is reviewed in Krywicki and Yee, *Breast Cancer Research and Treatment*, 22:7-19, 1992.

IGF/IGF-1R driven disorders are characterized by inappropriate or over-activity of IGF/IGF-1R. Inappropriate IGF activity refers to either: (1) IGF or IGF-1R expression in cells which normally do not express IGF or IGF-1R; (2) increased IGF or IGF-1R expression leading to unwanted cell proliferation such as cancer; (3) increased IGF or IGF-1R activity leading to unwanted cell proliferation, such as cancer; and/or over-activity of IGF or IGF-1R. Over-activity of IGF or IGF-1R refers to either an amplification of the gene encoding IGF-1, IGF-2, IGF-1R or the production of a level of IGF activity which can be correlated with a cell proliferative disorder (i.e., as the level of IGF increases the severity of one or more of the symptoms of the cell proliferative disorder increases) the bioavailability of IGF-1 and IGF-2 can also be affected by the presence or absence of a set of IGF binding proteins (IGF BPs) of which there are six known. Over activity of IGF/IGF-1R can also result from a down regulation of IGF-2 which contains an IGF-2 binding domain, but no intracellular kinase domain.

Examples of IGF/IGF-1R driven disorders include the various IGF/IGF-1R related human malignancies reviewed in Cullen, *et al.*, *Cancer Investigation*, 9(4):443-454,

1991, incorporated herein by reference in its entirety, including any drawings. IGF/IGF-1Rs clinical importance and role in regulating osteoblast function is reviewed in Schmid, *Journal of Internal Medicine*, 234:535-542, 1993.

Thus, IGF-1R activities include: (1) phosphorylation of IGF-1R protein; (2) phosphorylation of an IGF-1R protein substrate; (3) interaction with an IGF adapter protein; (4) IGF-1R protein surface expression. Additional IGF-1R protein activities can be identified using standard techniques. IGF-1R activity can be assayed by measuring one or more of the following activities: (1) phosphorylation of IGF-1R; (2) phosphorylation of an IGF-1R substrate; (3) activation of an IGF-1R adapter molecule; and (4) activation of downstream signaling molecules, and/or (5) increased cell division. These activities can be measured using techniques described below and known in the arts.

IGF-1R has been implicated as an absolute requirement for the establishment and maintenance of the transformed phenotype both *in vitro* and *in vivo* in several cell types (R. Baserga, *Cancer Research* 55:249-252, 1995). Herbimycin A has been said to inhibit the IGF-1R protein tyrosine kinase and cellular proliferation in human breast cancer cells (Sepp-Lorenzino, et al., 1994, *J. Cell Biochem. Suppl.* 18b: 246). Experiments studying the role of IGF-1R in transformation have used antisense strategies, dominant negative mutants, and antibodies to the IGF-1R and have led to the suggestion that IGF-1R may be a preferred target for therapeutic interventions.

IGF-1R, in addition to being implicated in nutritional support and in type-II diabetes, has also been associated with several types of cancers. For example, IGF-1 has been implicated as an autocrine growth stimulator for several tumor types, e.g. human breast cancer carcinoma cells (Arteaga et al., *J. Clin. Invest.*, 1989, 84:1418-1423) and small lung tumor cells (Macauley et al., *Cancer Res.*, 1989, 50:2511-2517). In addition, IGF-1, while integrally involved in the normal growth and differentiation of the nervous system, also appears to be an autocrine stimulator of human gliomas. Sandberg-Nordqvist et al., *Cancer Res.*, 1993, 53:2475-2478.

An example of IGF-2's protential involvement in colorectal cancer may be found in the up-regulation of IGF-2 mRNA in colon tumors relative to normal color tissue. (Zhang et al., Science (1997) 276:1268-1272.) IGF-2 may also play a role in hypoxia induced neovascularization of tumors. (Minet et al., Int. J. Mol. Med. 5 (2000) 5:253-259.) IGF-2 may also play a role in tumorigenesis through activation of an insulin receptor isoform-A. IGF-2 activation of insulin receptor isoform-A activates cell survival signaling pathways in cells but its relative contribution to tumor cell growth and survival is unknown at this time. Insulin receptor isoform-A's kinase domain is identical to the standard insulin receptor's. Scalia et al., 2001, J. Cell Biochem. 82:610-618.

The importance of IGF-1R and its ligands in cell types in culture (fibroblasts, epithelial cells, smooth muscle cells, T-lymphocytes, myeloid cells, chondrocytes and osteoblasts (the stem cells of the bone marrow)) is illustrated by the ability of IGF-1 to stimulate cell growth and proliferation. Goldring and Goldring, Eukaryotic Gene Expression, 1991, 1:301-326. In a series of recent publications, Baserga and others suggests that IGF-1R plays a central role in the mechanism of transformation and, as such, could be a preferred target for therapeutic interventions for a broad spectrum of human malignancies. Baserga, Cancer Res., 1995, 55:249-252; Baserga, Cell, 1994, 79:927-930; Coppola et al., Mol. Cell. Biol., 1994, 14:4588-4595; Baserga, Trends in Biotechnology, 1996, 14:150-152; H.M. Khandwala et al., Endocrine Reviews, 21:215-244, 2000. The predominant cancers that may be treated using a compound of the instant invention include, but are not limited to breast cancer, prostate cancer, colorectal cancer, small cell lung cancer, non-small cell lung cancer, renal cell carcinoma, or endometrial carcinoma.

IGF-1 has also been associated with retinal neovascularization. Proliferative diabetes retinopathy has been seen in some patients having high levels of IGF-1. (L.E. Smith et al., Nature Medicine, 1999, 5:1390-1395.)

Compounds of the instant invention may also be useful as anti-aging agents. It has been observed that there is a link between IGF signalling and aging. Experiments have shown that calorie-restricted mammals have low levels of insulin

and IGF-1 and have a longer life span. Similar observations have been made for insects as well. (See C. Kenyon, *Cell*, 2001, 105:165-168; E. Strauss, *Science*, 2001, 292:41-43; K.D. Kimura et al., *Science* 1997, 277:942-946; M. Tatar et al., *Science*, 2001, 292:107-110).

5 STKs have been implicated in many types of cancer including, notably, breast cancer (Cance et al., *Int. J. Cancer*, 1993, 54:571-77).

 The association between abnormal PK activity and disease is not restricted to cancer. For example, RTKs have been associated with diseases such as psoriasis, diabetes mellitus, endometriosis, angiogenesis, atheromatous plaque
10 development, Alzheimer's disease, epidermal hyperproliferation, neurodegenerative diseases, age-related macular degeneration and hemangiomas. For example, EGFR has been indicated in corneal and dermal wound healing. Defects in Insulin-R and IGF-1R are indicated in type-II diabetes mellitus. A more complete correlation between specific RTKs and their therapeutic indications is set forth in Plowman et al.,
15 DN&P, 1994, 7:334-339.

 As noted previously, not only RTKs but CTKs including, but not limited to, src, abl, fps, yes, fyn, lyn, lck, Zap70, blk, hck, fgr and yrk (reviewed by Bolen et al., *FASEB J.*, 1993, 6:3403-3409) are involved in the proliferative and metabolic signal transduction pathway and thus could be expected, and have been
20 shown, to be involved in may PTK-mediated disorders to which the present invention is directed. For example, mutated src (v-src) has been shown to be an oncoprotein (pp60^{v-src}) in chicken. Moreover, its cellular homolog, the protooncogene pp60^{c-src} transmits oncogenic signals of many receptors. Over-expression of EGFR or
25 HER2/neu in tumors leads to the constitutive activation of pp60^{c-src}, which is characteristic of malignant cells, but absent in normal cells. On the other hand, mice deficient in the expression of c-src exhibit an osteopetrotic phenotype, indicating a key participation of c-src in osteoclast function and a possible involvement in related disorders.

 Similarly, Zap70 has been implicated in T-cell signaling which may
30 relate to autoimmune disorders.

STKs have been associated with inflammation, autoimmune disease, immunoresponses, and hyperproliferation disorders such as restenosis, fibrosis, psoriasis, osteoarthritis and rheumatoid arthritis.

PKs have also been implicated in embryo implantation. Thus, the compounds of this invention may provide an effective method of preventing such embryo implantation and thereby be useful as birth control agents.

Finally, both RTKs and CTKs are currently suspected as being involved in hyperimmune disorders.

These and other aspects of the invention will be apparent from the teachings contained herein.

A method for identifying a chemical compound that modulates the catalytic activity of one or more of the above discussed protein kinases is another aspect of this invention. The method involved contacting cells expressing the desired protein kinase with a compound of this invention (or its salt or prodrug) and monitoring the cells for any effect that the compound has on them. The effect may be any observable, either to the naked eye or through the use of instrumentation, change or absence of change in a cell phenotype. The change or absence of change in the cell phenotype monitored may be, for example, without limitation, a change or absence of change in the catalytic activity of the protein kinase in the cells or a change or absence of change in the interaction of the protein kinase with a natural binding partner.

COMPOSITION

Pharmaceutical compositions of the above compounds are a further aspect of this invention.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The present invention also encompasses a pharmaceutical composition useful in the treatment of cancer, comprising the administration of a therapeutically

effective amount of the compounds of this invention, with or without pharmaceutically acceptable carriers or diluents. Suitable compositions of this invention include aqueous solutions comprising compounds of this invention and pharmacologically acceptable carriers, e.g., saline, at a pH level, e.g., 7.4. The solutions may be introduced into a patient's bloodstream by local bolus injection.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients, which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, microcrystalline cellulose, sodium crosscarmellose, corn starch, or alginic acid; binding agents, for example starch, gelatin, polyvinyl-pyrrolidone or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to mask the unpleasant taste of the drug or delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a water soluble taste masking material such as hydroxypropyl-methylcellulose or hydroxypropylcellulose, or a time delay material such as ethyl cellulose, cellulose acetate butyrate may be employed.

The compounds of the instant invention may also be co-administered with other well-known therapeutic agents that are selected for their particular usefulness against the condition that is being treated. For example, in the case of bone-related disorders, combinations that would be useful include those with

antiresorptive bisphosphonates, such as alendronate and risedronate; integrin blockers (defined further below), such as $\alpha_v\beta_3$ antagonists; conjugated estrogens used in hormone replacement therapy, such as PREMPRO®, PREMARIN® and ENDOMETRION®; selective estrogen receptor modulators (SERMs), such as
5 raloxifene, droloxifene, CP-336,156 (Pfizer) and lasofoxifene; cathepsin K inhibitors; and ATP proton pump inhibitors.

The instant compounds are also useful in combination with known anti-cancer agents. Such known anti-cancer agents include the following: estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators,
10 cytotoxic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors, HIV protease inhibitors, reverse transcriptase inhibitors, and other angiogenesis inhibitors. The instant compounds are particularly useful when coadministered with radiation therapy. The synergistic effects of inhibiting VEGF in combination with radiation therapy have been described in the art. (see WO
15 00/61186.)

“Estrogen receptor modulators” refers to compounds, which interfere or inhibit the binding of estrogen to the receptor, regardless of mechanism. Examples of estrogen receptor modulators include, but are not limited to, tamoxifen, raloxifene, idoxifene, LY353381, LY117081, toremifene, fulvestrant, 4-[7-(2,2-dimethyl-1-oxopropoxy-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-2H-1-benzopyran-3-yl)-phenyl-2,2-dimethylpropanoate, 4,4'-dihydroxybenzophenone-2,4-dinitrophenyl-hydrazone, and SH646.
20

“Androgen receptor modulators” refers to compounds which interfere or inhibit the binding of androgens to the receptor, regardless of mechanism.
25 Examples of androgen receptor modulators include finasteride and other 5 α -reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole, and abiraterone acetate.

“Retinoid receptor modulators” refers to compounds, which interfere or inhibit the binding of retinoids to the receptor, regardless of mechanism. Examples of such retinoid receptor modulators include bexarotene, tretinoin, 13-cis-retinoic

acid, 9-cis-retinoic acid, α -difluoromethylornithine, ILX23-7553, trans-N-(4'-hydroxyphenyl) retinamide, and N-4-carboxyphenyl retinamide.

"Cytotoxic agents" refer to compounds which cause cell death primarily by interfering directly with the cell's functioning or inhibit or interfere with
 5 cell myosis, including alkylating agents, tumor necrosis factors, intercalators, microtubulin inhibitors, and topoisomerase inhibitors.

Examples of cytotoxic agents include, but are not limited to, tirapazimine, sertenef, cachectin, ifosfamide, tasonermin, lonidamine, carboplatin, doxorubicin, altretamine, prednimustine, dibromodulcitol, ranimustine, fotemustine,
 10 nedaplatin, oxaliplatin, temozolomide, heptaplatin, estramustine, improsulfan tosilate, trofosfamide, nimustine, dibrospidium chloride, pumitepa, lobaplatin, satraplatin, profiromycin, cisplatin, irofulven, dexifosfamide, cis-aminedichloro(2-methylpyridine) platinum, benzylguanine, glufosfamide, GPX100, (trans, trans, trans)-bis-mu-(hexane-1,6-diamine)-mu-[diamine-platinum(II)]bis[diamine(chloro) platinum
 15 (II)]tetrachloride, diarizidinylspermine, arsenic trioxide, 1-(11-dodecylamino-10-hydroxyundecyl)-3,7-dimethylxanthine, zorubicin, idarubicin, daunorubicin, bisantrene, mitoxantrone, pirarubicin, pinafide, valrubicin, amrubicin, antineoplaston, 3'-deamino-3'-morpholino-13-deoxo-10-hydroxycarminomycin, annamycin, galarubicin, elinafide, MEN10755, and 4-demethoxy-3-deamino-3-aziridiny-4-
 20 methylsulphonyl-daunorubicin (see WO 00/50032).

Examples of microtubulin inhibitors include paclitaxel, vindesine sulfate, 3',4'-didehydro-4'-deoxy-8'-norvincal leukoblastine, docetaxol, rhizoxin, dolastatin, mivobulin isethionate, auristatin, cemadotin, RPR109881, BMS184476, vinflunine, cryptophycin, 2,3,4,5,6-pentafluoro-N-(3-fluoro-4-methoxyphenyl)
 25 benzene sulfonamide, anhydrovinblastine, N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-L-proline-t-butylamide, TDX258, and BMS188797.

Some examples of topoisomerase inhibitors are topotecan, hycaptamine, irinotecan, rubitecan, 6-ethoxypropionyl-3',4'-O-exo-benzylidene-chartreusin, 9-methoxy-N,N-dimethyl-5-nitropyrazolo[3,4,5-kl]acridine-2-(6H)
 30 propanamine, 1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-

benzo[de]pyrano[3',4':b,7]indolizino[1,2b]quinoline-10,13(9H,15H)dione, lurtotecan, 7-[2-(N-isopropylamino)ethyl]-(20S)camptothecin, BNP1350, BNPI1100, BN80915, BN80942, etoposide phosphate, teniposide, sobuzoxane, 2'-dimethylamino-2'-deoxy-etoposide, GL331, N-[2-(dimethylamino)ethyl]-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide, asulacrine, (5a, 5aB, 8aa,9b)-9-[2-[N-[2-(dimethylamino)ethyl]-N-methylamino]ethyl]-5-[4-hydroxy-3,5-dimethoxyphenyl]-5,5a,6,8,8a,9-hexahydrofuro(3',4':6,7)naphtho(2,3-d)-1,3-dioxol-6-one, 2,3-(methylenedioxy)-5-methyl-7-hydroxy-8-methoxybenzo[c]-phenanthridinium, 6,9-bis[(2-aminoethyl)amino]benzo[g]isoguinoline-5,10-dione, 5-(3-aminopropylamino)-7,10-dihydroxy-2-(2-hydroxyethylaminomethyl)-6H-pyrazolo[4,5,1-de]acridin-6-one, N-[1-[2(diethylamino)ethylamino]-7-methoxy-9-oxo-9H-thioxanthen-4-ylmethyl]formamide, N-(2-(dimethylamino)ethyl)acridine-4-carboxamide, 6-[[2-(dimethylamino)ethyl]amino]-3-hydroxy-7H-indeno[2,1-c]quinolin-7-one, and dimesna.

15 “Antiproliferative agents” includes antisense RNA and DNA oligonucleotides such as G3139, ODN698, RVASKRAS, GEM231, and INX3001, and antimetabolites such as enocitabine, carmofur, tegafur, pentostatin, doxifluridine, trimetrexate, fludarabine, capecitabine, galocitabine, cytarabine ocfosfate, fosteabine sodium hydrate, raltitrexed, paltitrexid, emitefur, tiazofurin, decitabine, nolatrexed, pemetrexed, nelzarabine, 2'-deoxy-2'-methylidenecytidine, 2'-fluoromethylene-2'-deoxycytidine, N-[5-(2,3-dihydro-benzofuryl)sulfonyl]-N'-(3,4-dichlorophenyl)urea, N6-[4-deoxy-4-[N2-[2(E),4(E)-tetradecadienoyl]glycylamino]-L-glycero-B-L-mannoheptopyranosyl]adenine, aplidine, ecteinascidin, troxacitabine, 4-[2-amino-4-oxo-4,6,7,8-tetrahydro-3H-pyrimidino[5,4-b][1,4]thiazin-6-yl-(S)-ethyl]-2,5-thienoyl-L-glutamic acid, aminopterin, 5-fluorouracil, alanosine, 11-acetyl-8-(carbamoyloxymethyl)-4-formyl-6-methoxy-14-oxa-1,11-diazatetracyclo(7.4.1.0.0)-tetradeca-2,4,6-trien-9-yl acetic acid ester, swainsonine, lometrexol, dexrazoxane, methioninase, 2'-cyano-2'-deoxy-N4-palmitoyl-1-B-D-arabino furanosyl cytosine, and 3-aminopyridine-2-carboxaldehyde thiosemicarbazone. “Antiproliferative agents” also includes monoclonal antibodies to growth factors, other than those listed

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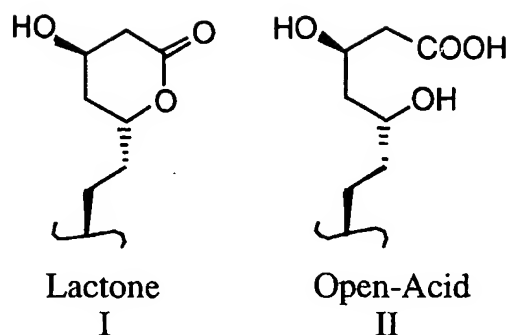
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under "angiogenesis inhibitors", such as trastuzumab, and tumor suppressor genes, such as p53, which can be delivered via recombinant virus-mediated gene transfer (see U.S. Patent No. 6,069,134, for example).

"HMG-CoA reductase inhibitors" refers to inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase. Compounds which have inhibitory activity for HMG-CoA reductase can be readily identified by using assays well-known in the art. For example, see the assays described or cited in U.S. Patent 4,231,938 at col. 6, and WO 84/02131 at pp. 30-33. The terms "HMG-CoA reductase inhibitor" and "inhibitor of HMG-CoA reductase" have the same meaning when used herein.

Examples of HMG-CoA reductase inhibitors that may be used include, but are not limited to, lovastatin (MEVACOR[®], see U.S. Patent Nos. 4,231,938, 4,294,926 and 4,319,039); simvastatin (ZOCOR[®], see U.S. Patent Nos. 4,444,784, 4,820,850 and 4,916,239); pravastatin (PRAVACHOL[®], see U.S. Patent Nos. 4,346,227, 4,537,859, 4,410,629, 5,030,447 and 5,180,589); fluvastatin (LESCOL[®], see U.S. Patent Nos. 5,354,772, 4,911,165, 4,929,437, 5,189,164, 5,118,853, 5,290,946 and 5,356,896); atorvastatin (LIPITOR[®], see U.S. Patent Nos. 5,273,995, 4,681,893, 5,489,691 and 5,342,952); and cerivastatin (also known as rivastatin and BAYCHOL[®], see US Patent No. 5,177,080). The structural formulae of these and additional HMG-CoA reductase inhibitors that may be used in the instant methods are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", *Chemistry & Industry*, pp. 85-89 (5 February 1996) and US Patent Nos. 4,782,084 and 4,885,314. The term HMG-CoA reductase inhibitor as used herein includes all pharmaceutically acceptable lactone and open-acid forms (i.e., where the lactone ring is opened to form the free acid) as well as salt and ester forms of compounds which have HMG-CoA reductase inhibitory activity, and therefor the use of such salts, esters, open-acid and lactone forms is included within the scope of this invention. An illustration of the lactone portion and its corresponding open-acid form is shown below as structures I and II.



In HMG-CoA reductase inhibitors where an open-acid form can exist, salt and ester forms may preferably be formed from the open-acid, and all such forms are included within the meaning of the term "HMG-CoA reductase inhibitor" as used

5 herein. Preferably, the HMG-CoA reductase inhibitor is selected from lovastatin and simvastatin, and most preferably simvastatin. Herein, the term "pharmaceutically acceptable salts" with respect to the HMG-CoA reductase inhibitor shall mean non-toxic salts of the compounds employed in this invention which are generally prepared by reacting the free acid with a suitable organic or inorganic base, particularly those

10 formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc and tetramethylammonium, as well as those salts formed from amines such as ammonia, ethylenediamine, N-methylglucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chlorprocaine, diethanolamine, procaine, N-benzylphenethylamine, 1-p-chlorobenzyl-2-pyrrolidine-1'-yl-methylbenz-

15 imidazole, diethylamine, piperazine, and tris(hydroxymethyl) aminomethane. Further examples of salt forms of HMG-CoA reductase inhibitors may include, but are not limited to, acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate,

20 glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, pamaote, palmitate, panthothenate, phosphate/diphosphate,

polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate.

Ester derivatives of the described HMG-CoA reductase inhibitor compounds may act as prodrugs which, when absorbed into the bloodstream of a warm-blooded animal, may cleave in such a manner as to release the drug form and permit the drug to afford improved therapeutic efficacy.

“Prenyl-protein transferase inhibitor” refers to a compound which inhibits any one or any combination of the prenyl-protein transferase enzymes, including farnesyl-protein transferase (FPTase), geranylgeranyl-protein transferase type I (GGPTase-I), and geranylgeranyl-protein transferase type-II (GGPTase-II, also called Rab GGPTase). Examples of prenyl-protein transferase inhibiting compounds include (+)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl) methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone, (-)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone, (+)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl) methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone, 5(*S*)-*n*-butyl-1-(2,3-dimethylphenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone, (*S*)-1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl)methyl]-2-piperazinone, 5(*S*)-*n*-Butyl-1-(2-methylphenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone, 1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)-2-methyl-5-imidazolylmethyl]-2-piperazinone, 1-(2,2-diphenylethyl)-3-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbonyl]piperidine, 4-{5-[4-hydroxymethyl-4-(4-chloropyridin-2-ylmethyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl} benzonitrile, 4-{5-[4-hydroxymethyl-4-(3-chlorobenzyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl} benzonitrile, 4-{3-[4-(2-oxo-2H-pyridin-1-yl)benzyl]-3H-imidazol-4-ylmethyl} benzonitrile, 4-{3-[4-(5-chloro-2-oxo-2H-[1,2']bipyridin-5'-ylmethyl)-3H-imidazol-4-ylmethyl} benzonitrile, 4-{3-[4-(2-oxo-2H-[1,2']bipyridin-5'-ylmethyl)-3H-imidazol-4-ylmethyl} benzonitrile, 4-[3-(2-oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl} benzonitrile, 18,19-dihydro-19-oxo-5*H*,17*H*-6,10:12,16-dimetheno-1H-imidazo[4,3-*c*][1,11,4]dioxazacyclo -

nonadecine-9-carbonitrile, (\pm)-19,20-dihydro-19-oxo-5*H*-18,21-ethano-12,14-etheno-6,10-metheno-22*H*-benzo[*d*]imidazo[4,3-*k*][1,6,9,12]oxatriaza-cyclooctadecine-9-carbonitrile, 19,20-dihydro-19-oxo-5*H*,17*H*-18,21-ethano-6,10:12,16-dimetheno-22*H*-imidazo[3,4-*h*][1,8,11,14]oxatriazacycloeicosine-9-carbonitrile, and (\pm)-19,20-
 5 dihydro-3-methyl-19-oxo-5*H*-18,21-ethano-12,14-etheno-6,10-metheno-22*H*-benzo[*d*]imidazo[4,3-*k*][1,6,9,12]oxa-triazacyclooctadecine-9-carbonitrile.

Other examples of prenyl-protein transferase inhibitors can be found in the following publications and patents: WO 96/30343, WO 97/18813, WO 97/21701, WO 97/23478, WO 97/38665, WO 98/28980, WO 98/29119, WO 95/32987, U.S. Patent No. 5,420,245, U.S. Patent No. 5,523,430, U.S. Patent No. 5,532,359, U.S. Patent No. 5,510,510, U.S. Patent No. 5,589,485, U.S. Patent No. 5,602,098, European Patent Publ. 0 618 221, European Patent Publ. 0 675 112, European Patent Publ. 0 604 181, European Patent Publ. 0 696 593, WO 94/19357, WO 95/08542, WO 95/11917, WO 95/12612, WO 95/12572, WO 95/10514, U.S. Patent No. 5,661,152, WO 95/10515, WO 95/10516, WO 95/24612, WO 95/34535, WO 95/25086, WO 96/05529, WO 96/06138, WO 96/06193, WO 96/16443, WO 96/21701, WO 96/21456, WO 96/22278, WO 96/24611, WO 96/24612, WO 96/05168, WO 96/05169, WO 96/00736, U.S. Patent No. 5,571,792, WO 96/17861, WO 96/33159, WO 96/34850, WO 96/34851, WO 96/30017, WO 96/30018, WO 96/30362, WO 96/30363, WO 96/31111, WO 96/31477, WO 96/31478, WO 96/31501, WO 97/00252, WO 97/03047, WO 97/03050, WO 97/04785, WO 97/02920, WO 97/17070, WO 97/23478, WO 97/26246, WO 97/30053, WO 97/44350, WO 98/02436, and U.S. Patent No. 5,532,359.

For an example of the role of a prenyl-protein transferase inhibitor on angiogenesis see European J. of Cancer, Vol. 35, No. 9, pp.1394-1401 (1999).

Examples of HIV protease inhibitors include amprenavir, abacavir, CGP-73547, CGP-61755, DMP-450, indinavir, nelfinavir, tipranavir, ritonavir, saquinavir, ABT-378, AG 1776, and BMS-232,632. Examples of reverse transcriptase inhibitors include delaviridine, efavirenz, GS-840, HB Y097, lamivudine, nevirapine, AZT, 3TC, ddC, and ddI.

“Angiogenesis inhibitors” refers to compounds that inhibit the formation of new blood vessels, regardless of mechanism. Examples of angiogenesis inhibitors include, but are not limited to, tyrosine kinase inhibitors, such as inhibitors of the tyrosine kinase receptors Flt-1 (VEGFR1) and Flk-1/KDR (VEGFR20),

5 inhibitors of epidermal-derived, fibroblast-derived, or platelet derived growth factors, MMP (matrix metalloprotease) inhibitors, integrin blockers, interferon- α , interleukin-12, pentosan polysulfate, cyclooxygenase inhibitors, including nonsteroidal anti-inflammatories (NSAIDs) like aspirin and ibuprofen as well as selective cyclooxygenase-2 inhibitors like celecoxib and rofecoxib (PNAS, Vol. 89, p. 7384 (1992);

10 JNCI, Vol. 69, p. 475 (1982); Arch. Ophthalmol., Vol. 108, p.573 (1990); Anat. Rec., Vol. 238, p. 68 (1994); FEBS Letters, Vol. 372, p. 83 (1995); Clin. Orthop. Vol. 313, p. 76 (1995); J. Mol. Endocrinol., Vol. 16, p.107 (1996); Jpn. J. Pharmacol., Vol. 75, p. 105 (1997); Cancer Res., Vol. 57, p. 1625 (1997); Cell, Vol. 93, p. 705 (1998); Intl. J. Mol. Med., Vol. 2, p. 715 (1998); J. Biol. Chem., Vol. 274, p. 9116 (1999)),

15 carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin-1, angiotensin II antagonists (see Fernandez *et al.*, J. Lab. Clin. Med. 105:141-145 (1985)), and antibodies to VEGF. (see, Nature Biotechnology, Vol. 17, pp.963-968 (October 1999); Kim *et al.*, Nature, 362, 841-844 (1993); WO 00/44777; and WO 00/61186).

20 As described above, the combinations with NSAID's are directed to the use of NSAID's which are potent COX-2 inhibiting agents. For purposes of this specification an NSAID is potent if it possess an IC₅₀ for the inhibition of COX-2 of 1 μ M or less as measured by the cell or microsomal assay disclosed herein.

The invention also encompasses combinations with NSAID's which

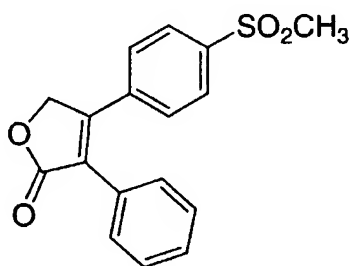
25 are selective COX-2 inhibitors. For purposes of this specification NSAID's which are selective inhibitors of COX-2 are defined as those which possess a specificity for inhibiting COX-2 over COX-1 of at least 100 fold as measured by the ratio of IC₅₀ for COX-2 over IC₅₀ for COX-1 evaluated by the cell or microsomal assay disclosed hereinunder. Such compounds include, but are not limited to those disclosed in U.S.

30 5,474,995, issued December 12, 1995, U.S. 5,861,419, issued January 19, 1999, U.S.

6,001,843, issued December 14, 1999, U.S. 6,020,343, issued February 1, 2000, U.S.
5,409,944, issued April 25, 1995, U.S. 5,436,265, issued July 25, 1995, U.S.
5,536,752, issued July 16, 1996, U.S. 5,550,142, issued August 27, 1996, U.S.
5,604,260, issued February 18, 1997, U.S. 5,698,584, issued December 16, 1997, U.S.
5 5,710,140, issued January 20, 1998, WO 94/15932, published July 21, 1994, U.S.
5,344,991, issued June 6, 1994, U.S. 5,134,142, issued July 28, 1992, U.S. 5,380,738,
issued January 10, 1995, U.S. 5,393,790, issued February 20, 1995, U.S. 5,466,823,
issued November 14, 1995, U.S. 5,633,272, issued May 27, 1997,
and U.S. 5,932,598, issued August 3, 1999, all of which are hereby incorporated by
10 reference.

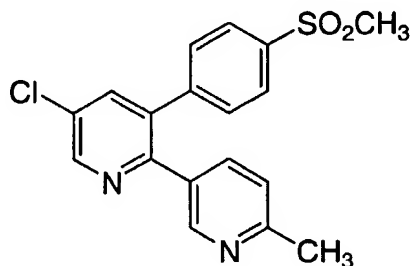
Inhibitors of COX-2 that are particularly useful in the instant method
of treatment are:

3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone; and



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5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(2-methyl-5-pyridinyl)pyridine;

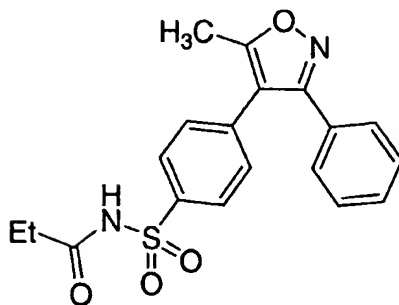
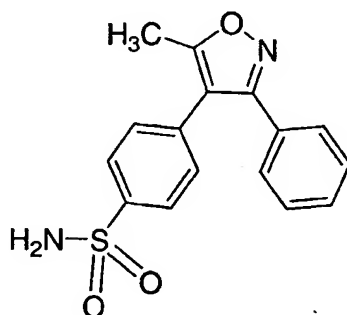
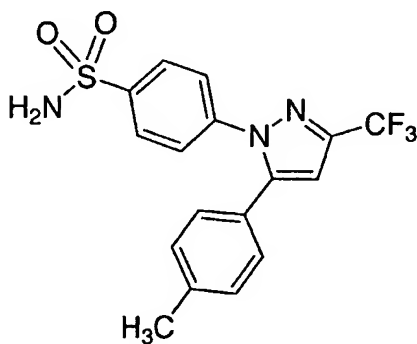


or a pharmaceutically acceptable salt thereof.

General and specific synthetic procedures for the preparation of the
20 COX-2 inhibitor compounds described above are found in U.S. Patent No. 5,474,995,

issued December 12, 1995, U.S. Patent No. 5,861,419, issued January 19, 1999, and U.S. Patent No. 6,001,843, issued December 14, 1999, all of which are herein incorporated by reference.

Compounds that have been described as specific inhibitors of COX-2
5 and are therefore useful in the present invention include, but are not limited to, the following:



10 or a pharmaceutically acceptable salt thereof.

Compounds, which are described as specific inhibitors of COX-2 and are therefore useful in the present invention, and methods of synthesis thereof, can be found in the following patents, pending applications and publications, which are herein incorporated by reference: WO 94/15932, published July 21, 1994, U.S. Patent
5 No. 5,344,991, issued June 6, 1994, U.S. Patent No. 5,134,142, issued July 28, 1992, U.S. Patent No. 5,380,738, issued January 10, 1995, U.S. Patent No. 5,393,790, issued February 20, 1995, U.S. Patent No. 5,466,823, issued November 14, 1995, U.S. Patent No. 5,633,272, issued May 27, 1997, and U.S. Patent No. 5,932,598, issued August 3, 1999.

10 Compounds which are specific inhibitors of COX-2 and are therefore useful in the present invention, and methods of synthesis thereof, can be found in the following patents, pending applications and publications, which are herein incorporated by reference: U.S. Patent No. 5,474,995 issued December 12, 1995, U.S. Patent No. 5,861,419 issued January 19, 1999, U.S. Patent No. 6,001,843 issued
15 December 14, 1999, U.S. Patent No. 6,020,343 issued February 1, 2000, U.S. Patent No. 5,409,944 issued April 25, 1995, U.S. Patent No. 5,436,265 issued July 25, 1995, U.S. Patent No. 5,536,752 issued July 16, 1996, U.S. Patent No. 5,550,142 issued August 27, 1996, U.S. Patent No. 5,604,260 issued February 18, 1997, U.S. Patent No. 5,698,584 issued December 16, 1997, and U.S. Patent No. 5,710,140 issued
20 January 20, 1998.

Other examples of angiogenesis inhibitors include, but are not limited to, endostatin, endostatin, ranpirinase, IM862, 5-methoxy-4-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-1-oxaspiro[2,5]oct-6-yl(chloroacetyl)carbamate, acetyldinanaline, 5-amino-1-[[3,5-dichloro-4-(4-chlorobenzoyl)phenyl]methyl]-1H-1,2,3-triazole-4-
25 carboxamide, CM101, squalamine, combretastatin, RPI4610, NX31838, sulfated mannopentaose phosphate, 7,7-(carbonyl-bis[imino-N-methyl-4,2-pyrrolocarbonyl-imino[N-methyl-4,2-pyrrole]-carbonylimino]-bis-(1,3-naphthalene disulfonate), and 3-[(2,4-dimethylpyrrol-5-yl)methylene]-2-indolinone (SU5416).

As used above, "integrin blockers" refers to compounds which
30 selectively antagonize, inhibit or counteract binding of a physiological ligand to the

$\alpha_v\beta_3$ integrin, to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha_v\beta_5$ integrin, to compounds which antagonize, inhibit or counteract binding of a physiological ligand to both the $\alpha_v\beta_3$ integrin and the $\alpha_v\beta_5$ integrin, and to compounds which antagonize, inhibit or counteract the activity of the particular integrin(s) expressed on capillary endothelial cells. The term also refers to antagonists of the $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins. The term also refers to antagonists of any combination of $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins.

Some specific examples of tyrosine kinase inhibitors include N-(trifluoromethylphenyl)-5-methylisoxazol-4-carboxamide, 3-[(2,4-dimethylpyrrol-5-yl)methylidenyl]indolin-2-one, 17-(allylamino)-17-demethoxygeldanamycin, 4-(3-chloro-4-fluorophenylamino)-7-methoxy-6-[3-(4-morpholinyl)propoxyl]quinazoline, N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, BIBX1382, 2,3,9,10,11,12-hexahydro-10-(hydroxymethyl)-10-hydroxy-9-methyl-9,12-epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocin-1-one, SH268, genistein, STI571, CEP2563, 4-(3-chlorophenylamino)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidinemethane sulfonate, 4-(3-bromo-4-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, 4-(4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, SU6668, STI571A, N-4-chlorophenyl-4-(4-pyridylmethyl)-1-phthalazinamine, and EMD121974.

The instant compounds are also useful, alone or in combination with platelet fibrinogen receptor (GP IIb/IIIa) antagonists, such as tirofiban, to inhibit metastasis of cancerous cells. Tumor cells can activate platelets largely via thrombin generation. This activation is associated with the release of VEGF. The release of VEGF enhances metastasis by increasing extravasation at points of adhesion to vascular endothelium (Amirkhosravi, *Platelets* 10, 285-292, 1999). Therefore, the present compounds can serve to inhibit metastasis, alone or in combination with GP IIb/IIIa) antagonists. Examples of other fibrinogen receptor antagonists include abciximab, eptifibatide, sibrafiban, lamifiban, lotrafiban, cromofiban, and CT50352.

FORMULATIONS

The compounds of this invention may be administered to mammals, preferably humans, either alone or, preferably, in combination with pharmaceutically acceptable carriers, excipients or diluents, optionally with known adjuvants, such as alum, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and/or topical routes of administration.

10 If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent(s) within its approved dosage range. Compounds of the instant invention may alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a combination formulation is inappropriate.

15 Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water soluble carrier such as polyethyleneglycol or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

20 For oral use of a compound according to this invention, particularly for chemotherapy, the selected compound may be administered, for example, in the form of tablets or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch, and lubricating agents, such as magnesium stearate, are commonly added. For oral administration in capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents may be added. For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient are usually

prepared, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled in order to render the preparation isotonic.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxyctanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as butylated hydroxyanisol or alpha-tocopherol.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example

sweetening, flavoring and coloring agents, may also be present. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavoring agents, preservatives and antioxidants.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, flavoring and coloring agents and antioxidant.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous solution. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution.

The sterile injectable preparation may also be a sterile injectable oil-in-water microemulsion where the active ingredient is dissolved in the oily phase. For example, the active ingredient may be first dissolved in a mixture of soybean oil and lecithin. The oil solution then introduced into a water and glycerol mixture and processed to form a microemulsion.

The injectable solutions or microemulsions may be introduced into a patient's bloodstream by local bolus injection. Alternatively, it may be advantageous to administer the solution or microemulsion in such a way as to maintain a constant circulating concentration of the instant compound. In order to maintain such a constant concentration, a continuous intravenous delivery device may be utilized. An example of such a device is the Deltec CADD-PLUS™ model 5400 intravenous pump.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension for intramuscular and subcutaneous administration. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents, which have been
5 mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butane diol. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. In
10 addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compounds of Formula I may also be administered in the form of a suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in
15 the rectum to release the drug. Such materials include cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compound of Formula I are employed. (For purposes of this
20 application, topical application shall include mouth washes and gargles.)

The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles and delivery devices, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal
25 delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen. Compounds of the present invention may also be delivered as a suppository employing bases such as cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

Additionally, the compounds of the instant invention may be administered to a mammal in need thereof using a gel extrusion mechanism (GEM) device, such as that described in U.S. Patent No. 4,976,697, filed on December 11, 1990, which is hereby incorporated by reference.

5 When a compound according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

In one exemplary application, a suitable amount of compound is
10 administered to a mammal undergoing treatment for cancer. Administration occurs in an amount between about 0.1 mg/kg of body weight to about 60 mg/kg of body weight per day, preferably of between 0.5 mg/kg of body weight to about 40 mg/kg of body weight per day.

The compounds of this invention may be prepared by employing
15 reactions as shown in the following schemes, in addition to other standard manipulations that are known in the literature or exemplified in the experimental procedures. These schemes, therefore, are not limited by the compounds listed nor by any particular substituents employed for illustrative purposes. Substituent numbering, as shown in the schemes, does not necessarily correlate to that used in the claims.

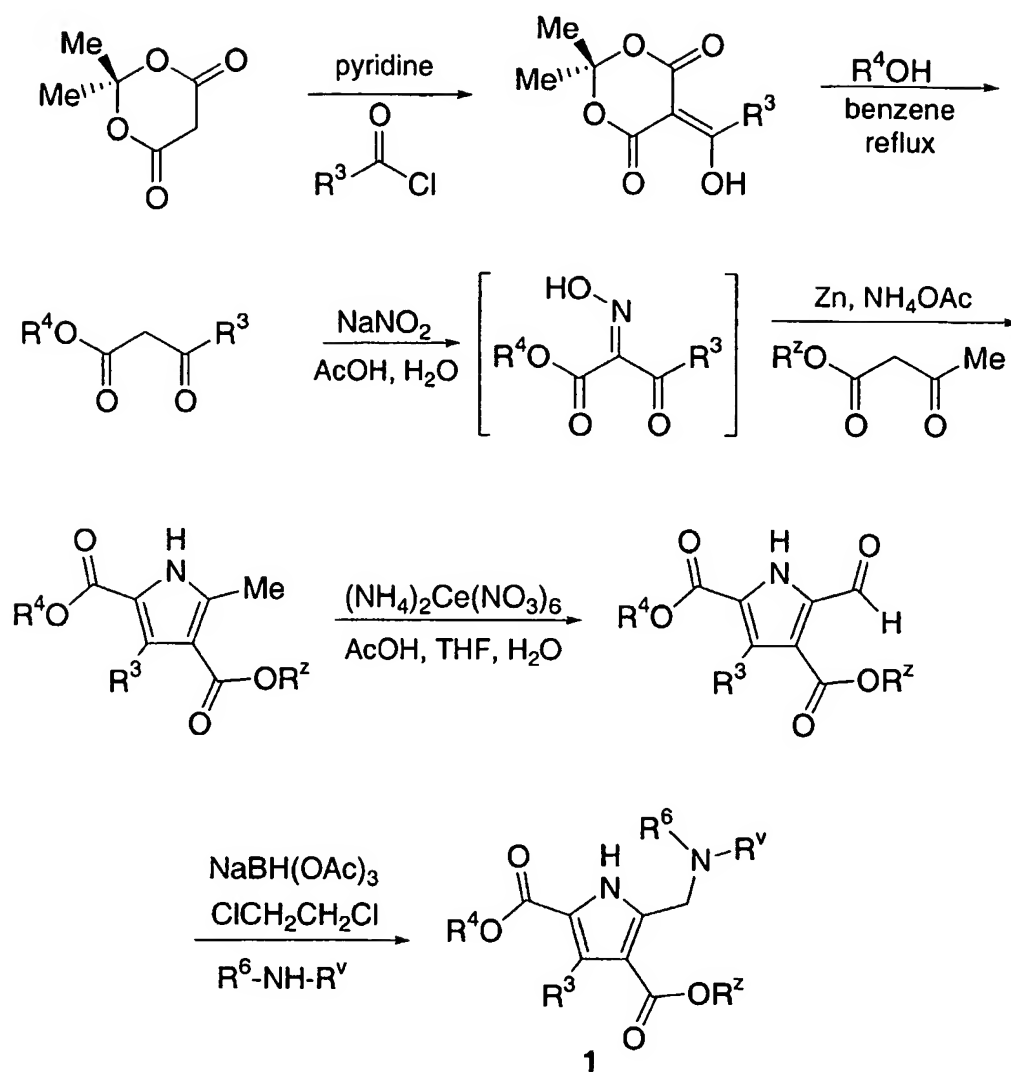
20 Scheme 1 details the synthesis of pyrrole 1. The illustrated synthesis of the required beta-ketoester intermediate utilizes the method of Yonemitsu, et al. (JOC (1978) Vol. 43, 2087-2088)

Scheme 2 illustrates the synthesis of pyrroles 4 and 5 using the intermediate pyrrole 3.

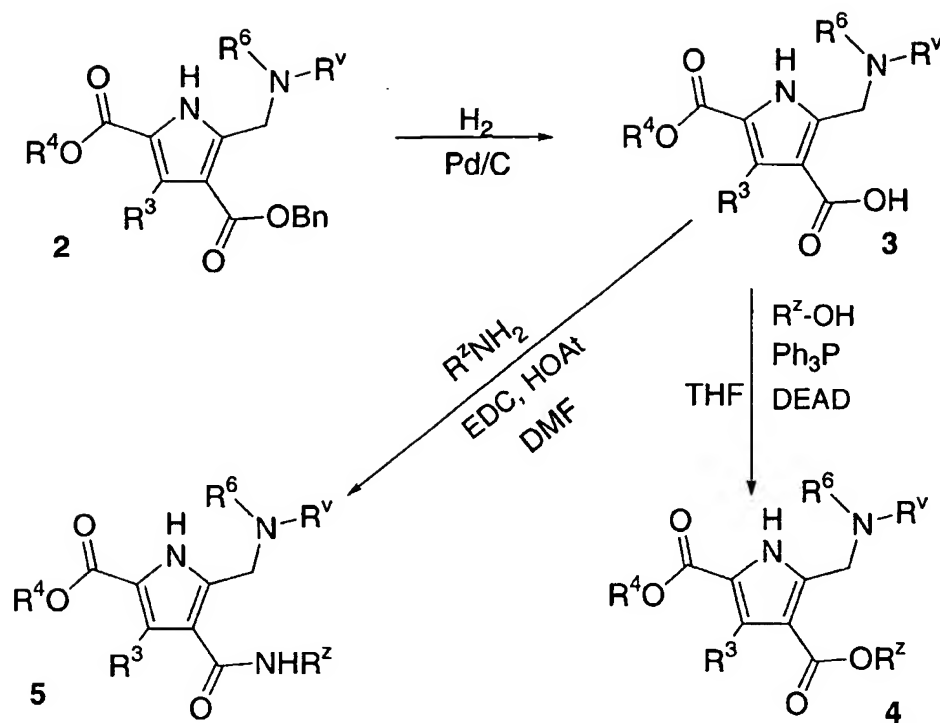
25 In the schemes below:

R^V represents $-\overset{\zeta}{\underset{\zeta}{-}}(CH_2)_p-V-(R^1)_r$, as described in Formula I; and R^Z represents OR^7 , $N(R^7)_2$, NHR^7OR^7 , $NH(CR^b_2)_qR^7$, $NHR^7NHC(O)R^7$, $NHR^7S(O)_2OR^7$, or $NH(CR^b_2)_qC(O)N(R^7)_2$ as described in Formula I.

SCHEME 1



SCHEME 2



5

EXAMPLES

Examples provided are intended to assist in a further understanding of the invention. Particular materials employed, species and conditions are intended to be further illustrative of the invention and not limiting of the reasonable scope thereof.

10

EXAMPLE 1

2-tert-butyl 4-ethyl 3-benzyl-5-[[[(4-chlorophenyl)amino]methyl]-1H-pyrrole-2,4-dicarboxylate

15

Step A: 5-(1-hydroxy-2-phenylethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione

A solution of Meldrum's acid (10 g, 69.4 mmol) in CH₂Cl₂ (170 mL) was cooled to 0°C. Pyridine (11.2 ml, 138.8 mmol) and phenylacetyl chloride (10.1 mL, 76.3 mmol) were added via syringe. The resulting solution was stirred at 0°C for 1 hour, then warmed to room temperature and stirred for 1 hour. The reaction was diluted with CH₂Cl₂ and washed with aq HCl (15 mL conc HCl in 200 mL water, 1 x) and water (1 x). The organic solution was dried over Na₂SO₄ and concentrated to give a dark red solid.

10 Step B: tert-butyl 3-oxo-4-phenylbutanoate

A solution of 5-(1-hydroxy-2-phenylethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (18.2 g, 69.4 mmol), t-BuOH (19.9 ml, 208 mmol) and benzene (400 ml) was heated at reflux for 6 hours. Concentration *in vacuo* gave a red liquid.

15 Step C: 2-tert-butyl 4-ethyl 3-benzyl-5-methyl-1H-pyrrole-2,4-dicarboxylate

To a 14°C solution of tert-butyl 3-oxo-4-phenylbutanoate (69.4 mmol) in AcOH (44 mL) was added NaNO₂ (4.55 g, 65.9 mmol) in 12 mL H₂O via cannula. The rate of addition was controlled such that the temperature was maintained below 0°C. The resulting orange brown solution was stirred at room temperature overnight, then added via cannula to a mixture of ethyl 3-oxobutanoate (9.7 ml, 76.3 mmol), NH₄OAc (13.4 g, 173.5 mmol), and Zn (14.1 g, 215.1 mmol) in 26 mL of AcOH. The rate of addition was controlled such that the temperature was maintained between 55 and 70°C. The resulting suspension was stirred overnight. 150 mL of ice water was added, and the suspension was filtered. The solids were rinsed thoroughly with CH₂Cl₂, then the aqueous solution was separated and washed once with CH₂Cl₂. The combined organic solutions were washed with saturated aqueous sodium bicarbonate (2 x), then dried over Na₂SO₄ and concentrated. Purification by flash chromatography gave a white solid.

Step D: 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate

To a solution of 2-tert-butyl 4-ethyl 3-benzyl-5-methyl-1H-pyrrole-2,4-dicarboxylate (2.75 mmol) in THF (32 mL), AcOH (40 mL), and H₂O (32 mL) was added CAN in one portion. The reaction was stirred at room temperature for 4 hours, then poured into water (500 mL) and extracted with CH₂Cl₂ (3 x 100 mL). The combined organic solutions were washed with saturated aqueous sodium bicarbonate (1 x 200 mL), dried over Na₂SO₄ and concentrated. Purification by flash chromatography gave a white solid.

10 Step E: 2-tert-butyl 4-ethyl 3-benzyl-5-[(4-chlorophenyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate

To a solution of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate (0.23 mmol) and 4-chloroaniline in dichloroethane (2 mL) was added Na(OAc)₃BH (68 mg, 0.32 mmol). The reaction was stirred overnight, then 1 ml of MeOH was added, and the mixture was concentrated *in vacuo*. The residue was taken up in acetonitrile, filtered, and purified by reverse phase HPLC to give a pale yellow solid. HRMS (ES) exact mass calcd for C₂₆H₂₉ClN₂O₄ (M+H⁺): 469.1889. Found 469.1859.

20 EXAMPLE 2

[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-[(5-oxopyrrolidin-2-yl)methyl]methanaminium trifluoroacetate

25 Step A: 5-(1-hydroxypropylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione

Following the procedures described in Example 1, Step A, but using propanoyl chloride in place of phenylacetyl chloride, the titled compound was obtained.

30

Step B: tert-butyl 3-oxopentanoate

Following the procedures described in Example 1, Step B, but using 5-(1-hydroxypropylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione in place of 5-(1-hydroxy-2-phenylethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione, the titled compound was
5 obtained.

Step C: 2-tert-butyl 4-ethyl 3-ethyl-5-methyl-1H-pyrrole-2,4-dicarboxylate

Following the procedures described in Example 1, Step C, but using tert-butyl 3-oxopentanoate in place of tert-butyl 3-oxo-4-phenylbutanoate, the titled
10 compound was obtained.

Step D: 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate

Following the procedures described in Example 1, Step D, but using 2-tert-butyl 4-ethyl 3-ethyl-5-methyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-methyl-1H-pyrrole-2,4-dicarboxylate, the titled compound
15 was obtained.

Step E: [5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-
N-[(5-oxopyrrolidin-2-yl)methyl]methanaminium trifluoroacetate

Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 5-(aminomethyl)pyrrolidin-2-one in place of 4-chloroaniline, the titled compound was obtained. HRMS
20 (ES) exact mass calcd for C₂₀H₃₁N₃O₅ (M+H⁺): 394.2355. Found 394.2355.

25

EXAMPLE 3

[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-(1H-indol-2-ylmethyl)methanaminium trifluoroacetate

30 Following the procedures described in Example 1, Step E, but using

2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 1-(1H-indol-2-yl) methanamine in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for $C_{24}H_{31}N_3O_4$ ($M+H^+$): 426.2308. Found 426.2388.

5

EXAMPLE 4

N-{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-3,4-dichlorobenzenaminium trifluoroacetate

10 Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 3,4-dichloroaniline in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for $C_{21}H_{26}Cl_2N_2O_4$ ($M+H^+$): 441.1343. Found 441.1344.

15

EXAMPLE 5

N-{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-4-methylbenzenaminium trifluoroacetate

20 Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 4-methylphenylamine in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for $C_{22}H_{30}N_2O_4$ ($M+H^+$): 387.2279. Found 387.2274.

25

EXAMPLE 6

N-{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-4-hydroxybenzenaminium trifluoroacetate

30 Following the procedures described in Example 1, Step E, but using

2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 4-aminophenol in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₁H₂₈N₂O₅ (M+H⁺): 389.2071. Found 389.2070.

5

EXAMPLE 7

N-{{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-4-methoxybenzenaminium trifluoroacetate

10 Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 4-methoxyaniline in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₂H₃₀N₂O₆ (M+H⁺): 403.2228. Found 403.2221.

15

EXAMPLE 8

N-{{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-4-chloro-N-methylbenzenaminium trifluoroacetate

20 Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 4-chloro-N-methylaniline in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₂H₂₉ClN₂O₄ (M+H⁺): 421.1889. Found 421.1895.

25

EXAMPLE 9

2-[[[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl]ammonio)methyl]-6-methylpyridinium bis(trifluoroacetate)

Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and (6-methylpyridin-2-yl)methylamine in place of 4-chloroaniline, the titled compound was
5 obtained. HRMS (ES) exact mass calcd for C₂₂H₃₁N₃O₄ (M+H⁺): 402.2388. Found 402.2386.

EXAMPLE 10

10 3-[[[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl]ammonio)methyl]-5-cyclopropyl-1H-pyrazol-1-ium bis(trifluoroacetate)

Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and (5-cyclopropyl-1H-pyrazol-3-yl)methylamine in place of 4-chloroaniline, the titled compound was
15 obtained. HRMS (ES) exact mass calcd for C₂₂H₃₂N₄O₄ (M+H⁺): 417.2497. Found 417.2481.

EXAMPLE 11

20

[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-[(3,5-dimethyl-1H-pyrazol-4-yl)methyl]methanaminium trifluoroacetate

Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and (3,5-dimethyl-1H-pyrazol-4-yl)methylamine in place of 4-chloroaniline, the titled compound was
25 obtained. HRMS (ES) exact mass calcd for C₂₁H₃₂N₄O₄ (M+H⁺): 405.2497. Found 405.2517.

30

EXAMPLE 12

[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-[(5-phenyl-1,3,4-oxadiazol-2-yl)methyl]methanaminium trifluoroacetate

- 5 Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and (5-phenyl-1,3,4-oxadiazol-2-yl)methylamine in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₄H₃₀N₄O₅ (M+H⁺): 455.2289.
- 10 Found 455.2293.

EXAMPLE 13

2-[(5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl)methyl}
15 ammonio)methyl]-1H-imidazol-1-ium bis(trifluoroacetate)

- Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 1-(1H-imidazol-2-yl)methanamine in place of 4-chloroaniline, the titled compound was obtained. HRMS
- 20 (ES) exact mass calcd for C₁₉H₂₈N₄O₄ (M+H⁺): 377.2184. Found 377.2170.

EXAMPLE 14

5-[(5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl)methyl}
25 ammonio)methyl]-3-methyl-4H-1,2,4-triazole-1,4-diiium tris(trifluoroacetate)

- Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and (5-methyl-4H-1,2,4-triazol-3-yl)methylamine in place of 4-chloroaniline, the titled compound was

obtained. HRMS (ES) exact mass calcd for C₁₉H₂₉N₅O₄ (M+H⁺): 392.2293.

Found 392.2292.

EXAMPLE 15

5

6-[[[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl]ammonio)methyl]-2-methylimidazo[2,1-b][1,3]thiazol-7-ium bis(trifluoroacetate)

Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and (2-methylimidazo[2,1-b][1,3]thiazol-6-yl)methylamine in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₂H₃₀N₄O₄S (M+H⁺): 447.2061. Found 447.2058.

15

EXAMPLE 16

2-[[[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl]ammonio)methyl]-4-methyl-1H-imidazol-3-ium bis(trifluoroacetate)

Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and (4-methyl-1H-imidazol-2-yl)methylamine in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₀H₃₀N₄O₄ (M+H⁺): 391.2340. Found 391.2332.

25

EXAMPLE 17

2-[[[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl]ammonio)methyl]-1-methyl-1H-imidazol-3-ium bis(trifluoroacetate)

Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and (1-methyl-1H-imidazol-2-yl)methylamine in place of 4-chloroaniline, the titled compound was
5 obtained. HRMS (ES) exact mass calcd for C₂₀H₃₀N₄O₄ (M+H⁺): 391.2340.
Found 391.2329.

EXAMPLE 18

10 [5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-[(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl]methanaminium trifluoroacetate

Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 5-(aminomethyl)-
15 2,4-dihydro-3H-1,2,4-triazol-3-one in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for C₁₈H₂₇N₅O₅ (M+H⁺): 394.2085.
Found 394.2074.

EXAMPLE 19

20

5-[(5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl)methyl]ammonio)methyl]-1H-1,2,4-triazol-1-ium bis(trifluoroacetate)

Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 1-(1H-1,2,4-triazol-5-yl)methanamine in place of 4-chloroaniline, the titled compound was
25 obtained. HRMS (ES) exact mass calcd for C₁₈H₂₇N₅O₄ (M+H⁺): 378.2136.
Found 378.2132.

30

EXAMPLE 20

6-[[[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl]ammonio)methyl]imidazo[2,1-b][1,3]thiazol-4-ium bis(trifluoroacetate)

- 5 Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 6-(aminomethyl)imidazo[2,1-b][1,3]thiazol-4-ium in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₁H₂₈N₄O₄S (M+H⁺): 433.1904.
- 10 Found 433.1879.

EXAMPLE 21

2-[[[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl]ammonio)methyl]-5-chloro-3H-benzimidazol-1-ium bis(trifluoroacetate)

- 15 Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and (6-chloro-1H-benzimidazol-2-yl)methylamine in place of 4-chloroaniline, the titled compound was
- 20 obtained. HRMS (ES) exact mass calcd for C₂₃H₂₉ClN₄O₄ (M+H⁺): 461.1950.
- Found 461.1945.

EXAMPLE 22

25 [5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-[(4-oxo-3,4-dihydrophthalazin-1-yl)methyl]methanaminium trifluoroacetate

- Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 4-(aminomethyl)
- 30 phthalazin-1(2H)-one in place of 4-chloroaniline, the titled compound was

obtained. HRMS (ES) exact mass calcd for $C_{24}H_{30}N_4O_5$ ($M+H^+$): 455.2289. Found 455.2286.

EXAMPLE 23

5

[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-(1H-indol-6-ylmethyl)methanaminium trifluoroacetate

Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 1-(1H-indol-6-yl)methanamine in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for $C_{24}H_{31}N_3O_4$ ($M+H^+$): 426.2388. Found 426.2365.

EXAMPLE 24

15

[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-[(4-methyl-1,3-thiazol-2-yl)methyl]methanaminium trifluoroacetate

Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and (4-methyl-1,3-thiazol-2-yl)methylamine in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for $C_{20}H_{29}N_3O_4S$ ($M+H^+$): 408.1952. Found 408.1968.

25

EXAMPLE 25

2-[[[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl]ammonio)methyl]-8-methylimidazo[1,2-a]pyridin-4-ium bis(trifluoroacetate)

Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-

butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and (8-methylimidazo [1,2-a]pyridin-2-yl)methylamine in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₄H₃₂N₄O₄ (M+H⁺): 441.2497.

Found 441.2466.

5

EXAMPLE 26

2-[[[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl} ammonio)methyl]-3H-benzimidazol-1-ium bis(trifluoroacetate)

10 Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 1-(1H-benzimidazol-2-yl)methanamine in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₃H₃₀N₄O₄ (M+H⁺): 427.2340.

15 Found 427.2332.

EXAMPLE 27

N-{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-3-
20 methylbenzenaminium trifluoroacetate

 Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 3-methylphenylamine in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES)
25 exact mass calcd for C₂₂H₃₀N₂O₄ (M+H⁺): 387.2279. Found 387.2275.

EXAMPLE 28

N-{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-4-
30 isopropylbenzenaminium trifluoroacetate

Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 4-isopropylaniline in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₄H₃₄N₂O₄ (M+H⁺): 415.2592. Found 415.2589.

EXAMPLE 29

N- {[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-4-ethylbenzenaminium trifluoroacetate

Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 4-ethylaniline in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₃H₃₂N₂O₄ (M+H⁺): 401.2435. Found 401.2479.

EXAMPLE 30

N- {[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-3,5-dimethylbenzenaminium trifluoroacetate

Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 3,5-dimethylaniline in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₃H₃₂N₂O₄ (M+H⁺): 401.2435. Found 401.2444.

EXAMPLE 31

N- {[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-3,4-dimethoxybenzenaminium trifluoroacetate

Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 3,4-dimethoxyaniline in place of 4-chloroaniline, the titled compound was
5 obtained. HRMS (ES) exact mass calcd for $C_{23}H_{32}N_2O_6$ ($M+H^+$): 433.2333. Found 433.2335.

EXAMPLE 32

10 2-[2-([5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl)methyl]ammonio)ethyl]pyridinium bis(trifluoroacetate)

Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 2-pyridin-2-
15 ylethanamine in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for $C_{22}H_{31}N_3O_4$ ($M+H^+$): 402.2388. Found 402.2412.

EXAMPLE 33

20 [5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-[(1-methyl-1H-pyrazol-4-yl)methyl]methanaminium trifluoroacetate

Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and (1-methyl-1H-
25 pyrazol-4-yl)methylamine in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for $C_{20}H_{30}N_4O_4$ ($M+H^+$): 391.2340. Found 391.2353.

EXAMPLE 34

N-{{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-4-ethoxybenzenaminium trifluoroacetate

5 Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 4-ethoxyaniline in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₃H₃₂N₂O₅ (M+H⁺): 417.2384. Found 417.2385.

10

EXAMPLE 35

N-{{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-3,4-dimethylbenzenaminium trifluoroacetate

15 Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 3,4-dimethylaniline in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₃H₃₂N₂O₄ (M+H⁺): 401.2435. Found 401.2431.

20

EXAMPLE 36

N-{{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-1,3-benzodioxol-5-aminium trifluoroacetate

25 Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 1,3-benzodioxol-5-amine in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₂H₂₈N₂O₆ (M+H⁺): 417.2020. Found 417.2022.

30

EXAMPLE 37

N-{{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-4-isopropoxybenzenaminium trifluoroacetate}

5 Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 4-isopropoxyaniline in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₄H₃₄N₂O₅ (M+H⁺): 431.2541. Found 431.2549.

10

EXAMPLE 38

4-[[[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl]ammonio)methyl]-1,3-thiazol-3-ium bis(trifluoroacetate)

15 Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 1,3-thiazol-4-ylmethylamine in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for C₁₉H₂₇N₃O₄S (M+H⁺): 394.1795. Found 394.1803.

20

EXAMPLE 39

5-[[[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl]ammonio)methyl]-1,3-thiazol-3-ium bis(trifluoroacetate)

25 Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 1,3-thiazol-5-ylmethylamine in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for C₁₉H₂₇N₃O₄S (M+H⁺): 394.1795.

30 Found 394.1803.

EXAMPLE 40

2-[[[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}
5 ammonio)methyl]-1,3-thiazol-3-ium bis(trifluoroacetate)

Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 1,3-thiazol-2-ylmethanamine in place of 4-chloroaniline, the titled compound was obtained. HRMS
10 (ES) exact mass calcd for C₁₉H₂₇N₃O₄S (M+H⁺): 394.1795.
Found 394.1803.

EXAMPLE 41

15 [5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-(isoxazol-5-ylmethyl)methanaminium trifluoroacetate

Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 1-isoxazol-5-ylmethanamine in place of 4-chloroaniline, the titled compound was obtained.
20 HRMS (ES) exact mass calcd for C₁₉H₂₇N₃O₅ (M+H⁺): 378.2024.
Found 378.2019.

EXAMPLE 42

25 [5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-[(1,5-dimethyl-1H-pyrazol-4-yl)methyl]methanaminium trifluoroacetate

Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and (1,5-dimethyl-1H-
30

pyrazol-4-yl)methylamine in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₁H₃₂N₄O₄ (M+H⁺): 405.2497. Found 405.2487.

5

EXAMPLE 43

N-([5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl)-4-
tert-butylbenzenaminium trifluoroacetate

Following the procedures described in Example 1, Step E, but using 2-
10 tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 4-tert-butylaniline in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₅H₃₆N₂O₄ (M+H⁺): 429.2748. Found 429.2749.

15

EXAMPLE 44

2-tert-butyl 4-ethyl 5-([4-(dimethylamino)phenyl]amino)methyl)-3-ethyl-1H-
pyrrole-2,4-dicarboxylate bis(trifluoroacetate)

Following the procedures described in Example 1, Step E, but using 2-
20 tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and N,N-dimethylbenzene-1,4-diamine in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₃H₃₃N₃O₄ (M+H⁺): 416.2544. Found 416.2553.

25

EXAMPLE 45

N-([5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl)-2-
methylbenzenaminium trifluoroacetate

Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 2-methylphenylamine in place of 4-chloroaniline, the titled compound was obtained.

- 5 HRMS (ES) exact mass calcd for $C_{22}H_{30}N_2O_4$ ($M+H^+$): 387.2279. Found 387.2282.

EXAMPLE 46

- 10 N-{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-2-methoxybenzenaminium trifluoroacetate

- Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 2-methoxyaniline
15 in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for $C_{22}H_{30}N_2O_5$ ($M+H^+$): 403.2228. Found 403.2226.

EXAMPLE 47

- 20 N-{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-4-propylbenzenaminium trifluoroacetate

- Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 4-propylaniline in
25 place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for $C_{24}H_{34}N_2O_4$ ($M+H^+$): 415.2592. Found 415.2600.

EXAMPLE 48

N- {[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-2,5-dimethoxybenzenaminium trifluoroacetate

5 Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 2,5-dimethoxyaniline in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₃H₃₂N₂O₆ (M+H⁺): 433.2333. Found 433.2346.

10

EXAMPLE 49

N- {[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-4-butylbenzenaminium trifluoroacetate

15 Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 4-butylaniline in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₅H₃₆N₂O₄ (M+H⁺): 429.2748. Found 429.2725.

20

EXAMPLE 50

N- {[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-3-hydroxy-4-methoxybenzenaminium trifluoroacetate

25 Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 5-amino-2-methoxyphenol in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₂H₃₀N₂O₆ (M+H⁺): 419.2177. Found 419.2183.

30

EXAMPLE 51

N- {[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-1H-indol-4-aminium trifluoroacetate

5 Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 1H-indol-4-amine in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₃H₂₉N₃O₄ (M+H⁺): 412.2231. Found 412.2233.

10

EXAMPLE 52

N- {[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-1H-indol-6-aminium trifluoroacetate

15 Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 1H-indol-6-amine in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₃H₂₉N₃O₄ (M+H⁺): 412.2231. Found 412.2219.

20

EXAMPLE 53

N- {[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-3-methoxypropan-1-aminium trifluoroacetate

25 Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 3-methoxypropan-1-amine in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for C₁₉H₃₂N₂O₅ (M+H⁺): 369.2384. Found 369.2367.

30

EXAMPLE 54

N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl)methyl}
ethanaminium trifluoroacetate

5 Following the procedures described in Example 1, Step E, but using 2-
tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-
butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and ethanamine in
place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass
calcd for C₁₇H₂₈N₂O₄ (M+H⁺): 325.2122. Found 325.2098.

10

EXAMPLE 55

N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl)methyl}
butan-1-aminium trifluoroacetate

15 Following the procedures described in Example 1, Step E, but using 2-
tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-
butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and butan-1-amine in
place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass
calcd for C₁₉H₃₂N₂O₄ (M+H⁺): 353.2435. Found 353.2416.

20

EXAMPLE 56

N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl)methyl}-3-
methoxybenzenaminium trifluoroacetate

25 Following the procedures described in Example 1, Step E, but using 2-
tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-
butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 3-methoxyaniline
in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact
mass calcd for C₂₂H₃₀N₂O₅ (M+H⁺): 403.2228. Found 403.2265.

30

EXAMPLE 57

N-{{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}}-3-carboxypropan-1-aminium trifluoroacetate

5 Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 4-aminobutanoic acid in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for C₁₉H₃₀N₂O₆ (M+H⁺): 383.2177. Found 383.2181.

10

EXAMPLE 58

[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-methylmethanaminium trifluoroacetate

15 Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and methanamine in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for C₁₆H₂₆N₂O₄ (M+H⁺): 311.1966. Found 311.1964.

20

EXAMPLE 59

N-{{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}}-2-methylpropan-1-aminium trifluoroacetate

25 Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 2-methylpropan-1-amine in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for C₁₉H₃₂N₂O₄ (M+H⁺): 353.2435. Found 353.2452.

30

EXAMPLE 60

N-{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}
pentan-1-aminium trifluoroacetate

5 Following the procedures described in Example 1, Step E, but using 2-
tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-
butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and pentan-1-amine in
place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass
calcd for C₂₀H₃₄N₂O₄ (M+H⁺): 367.2592. Found 367.2579.

10

EXAMPLE 61

2-(aminosulfonyl)-N-{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-
pyrrol-2-yl]methyl}ethanaminium trifluoroacetate

15 Following the procedures described in Example 1, Step E, but using 2-
tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-
butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and pentan-1-amine in
place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass
calcd for C₁₇H₂₉N₃O₆S (M+H⁺): 404.1850. Found 404.1841.

20

EXAMPLE 62

[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-(1H-pyrrol-2-
ylmethyl)methanaminium trifluoroacetate

25 Following the procedures described in Example 1, Step E, but using 2-
tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-
butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 1-(1H-pyrrol-2-
yl)methanamine in place of 4-chloroaniline, the titled compound was obtained.
HRMS (ES) exact mass calcd for C₂₀H₂₉N₃O₄ (M+H⁺): 376.2231. Found
30 376.2234.

EXAMPLE 63

N-([5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl)-4-chlorobenzenaminium chloride

5 Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate, the titled compound was obtained. HRMS (ES) exact mass calcd for $C_{21}H_{27}ClN_2O_4$ ($M+H^+$): 407.1732. Found 407.1729.

10

EXAMPLE 64

N-([5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl)-3-chlorobenzenaminium chloride

15 Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 3-chloroaniline in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for $C_{21}H_{27}ClN_2O_4$ ($M+H^+$): 407.1732. Found 407.1729.

20

EXAMPLE 65

N-([5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl)-2-chlorobenzenaminium chloride

25 Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 2-chloroaniline in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for $C_{21}H_{27}ClN_2O_4$ ($M+H^+$): 407.1732. Found 407.1731.

30

EXAMPLE 66

3-bromo-N-([5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]
methyl)benzenaminium chloride

5 Following the procedures described in Example 1, Step E, but using 2-
tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-
butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 3-bromoaniline in
place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass
calcd for C₂₁H₂₇BrN₂O₄ (M+H⁺): 451.1227. Found 451.1233.

10

EXAMPLE 67

2-bromo-N-([5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]
methyl)benzenaminium chloride

15 Following the procedures described in Example 1, Step E, but using 2-
tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-
butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 2-bromoaniline in
place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass
calcd for C₂₁H₂₇BrN₂O₄ (M+H⁺): 451.1227. Found 451.1232.

20

EXAMPLE 68

N-([5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl)-4-
fluorobenzenaminium chloride

25 Following the procedures described in Example 1, Step E, but using 2-
tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-
butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 4-fluoroaniline in
place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass
calcd for C₂₁H₂₇FN₂O₄ (M+H⁺): 391.2028. Found 391.2024.

30

EXAMPLE 69

N-([5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl)-3-fluorobenzenaminium chloride

5 Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 3-fluoroaniline in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₁H₂₇FN₂O₄ (M+H⁺): 391.2028. Found 391.2031.

10

EXAMPLE 70

N-([5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl)-2-fluorobenzenaminium chloride

15 Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 2-fluoroaniline in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₁H₂₇FN₂O₄ (M+H⁺): 391.2028. Found 391.2028.

20

EXAMPLE 71

3-([5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl)ammonio)pyridinium dichloride

25 Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and pyridin-3-amine in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₀H₂₇N₃O₄ (M+H⁺): 374.2074. Found 374.2063.

30

EXAMPLE 72

2-([5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl)
ammonio)-5-chloropyridinium dichloride

5 Following the procedures described in Example 1, Step E, but using 2-
tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-
butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 5-chloropyridin-2-
amine in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES)
exact mass calcd for $C_{20}H_{26}ClN_3O_4$ ($M+H^+$): 408.1685. Found 408.1680.

10

EXAMPLE 73

4-bromo-N-([5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]
methyl)benzenaminium chloride

15 Following the procedures described in Example 1, Step E, but using 2-
tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-
butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 4-bromoaniline in
place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass
calcd for $C_{21}H_{27}BrN_2O_4$ ($M+H^+$): 451.1227. Found 451.1230.

20

EXAMPLE 74

2-tert-butyl 4-methyl 3-ethyl-5-([(4-methoxyphenyl)amino]methyl)-1H-pyrrole-2,4-
dicarboxylate

25

Step A: 5-(1-hydroxypropylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione

 Following the procedures described in Example 1, Step A, but using
propanoyl chloride in place of phenylacetyl chloride, the titled compound was
obtained.

30

Step B: tert-butyl 3-oxopentanoate

Following the procedures described in Example 1, Step B, but using 5-(1-hydroxypropylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione in place of 5-(1-hydroxy-2-phenylethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione, the titled compound was
5 obtained.

Step C: 2-tert-butyl 4-methyl 3-ethyl-5-methyl-1H-pyrrole-2,4-dicarboxylate

Following the procedures described in Example 1, Step C, but using tert-butyl 3-oxopentanoate in place of tert-butyl 3-oxo-4-phenylbutanoate and methyl
10 3-oxobutanoate in place of ethyl 3-oxobutanoate, the titled compound was obtained.

Step D: 2-tert-butyl 4-methyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate

Following the procedures described in Example 1, Step D, but 2-tert-butyl 4-methyl 3-ethyl-5-methyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl
15 4-ethyl 3-benzyl-5-methyl-1H-pyrrole-2,4-dicarboxylate, the titled compound was obtained.

Step E: 2-tert-butyl 4-methyl 3-ethyl-5-[(4-methoxyphenyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate

Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-methyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 4-methoxyaniline in place of 4-chloroaniline, the titled compound was obtained. ¹H NMR (500 MHz, CDCl₃) δ 9.38 (br s, 1H); 6.76 (d, J = 8.8 Hz, 2H); 6.56 (d, J = 8.8 Hz, 2H); 4.57 (s, 2H); 4.00 (br s, 1H); 3.84 (s, 3H); 3.74 (s, 3H); 3.06 (q, J = 7.4 Hz, 2H); 1.54 (s, 9H);
25 1.17 (t, J = 7.3 Hz, 3H). HRMS (ES) exact mass calcd for C₂₁H₂₈N₂O₅ (M+H⁺): 389.2071. Found 389.2065.

EXAMPLE 75

N-([5-(tert-butoxycarbonyl)-4-ethyl-3-(methoxycarbonyl)-1H-pyrrol-2-yl]methyl)-4-pentylbenzenaminium trifluoroacetate

5 Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-methyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 4-pentylaniline in place of 4-chloroaniline, the titled compound was obtained. ¹H NMR (500 MHz, CD₃OD) δ 7.30 (d, J = 8.3 Hz, 2H); 7.17 (d, J = 8.5 Hz, 2H); 4.67 (s, 2H); 3.91 (s, 3H); 3.07 (q, J = 7.3 Hz, 2H); 2.63 (t, J = 7.7 Hz, 2H); 1.61 (m, 2H); 1.57 (s, 9H); 10 3H); 1.33 (m, 4H); 1.14 (t, J = 7.5 Hz, 3H); 0.90 (t, J = 7.2 Hz, 3H). HRMS (ES) exact mass calcd for C₂₅H₃₆N₂O₄ (M+H⁺): 429.2748. Found 429.277.

EXAMPLE 76

15 N-([5-(tert-butoxycarbonyl)-4-ethyl-3-(methoxycarbonyl)-1H-pyrrol-2-yl]methyl)-1,1'-biphenyl-4-aminium trifluoroacetate

 Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-methyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 1,1'-biphenyl-4-amine in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) 20 exact mass calcd for C₂₆H₃₀N₂O₄ (M+H⁺): 435.2279. Found 435.2274.

EXAMPLE 77

25 N-([5-(tert-butoxycarbonyl)-4-ethyl-3-(methoxycarbonyl)-1H-pyrrol-2-yl]methyl)-3,4,5-trimethoxybenzenaminium trifluoroacetate

 Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-methyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-

butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 3,4,5-trimethoxyaniline in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for $C_{23}H_{32}N_2O_7$ ($M+H^+$): 449.2283. Found 449.2291.

5

EXAMPLE 78

3-[4-([5-(tert-butoxycarbonyl)-4-ethyl-3-(methoxycarbonyl)-1H-pyrrol-2-yl)methyl]ammonio)phenyl]-5-methyl-4H-1,2,4-triazol-4-ium bis(trifluoroacetate)

- 10 Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-methyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 4-(5-methyl-4H-1,2,4-triazol-3-yl)aniline in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for $C_{23}H_{29}N_5O_4$ ($M+H^+$): 440.2293.
- 15 Found 440.2313.

EXAMPLE 79

[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-([2-(2R)-5-oxopyrrolidin-2-yl)methyl]methanaminium trifluoroacetate

- 20 Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and (5R)-5-(aminomethyl) pyrrolidin-2-one in place of 4-chloroaniline, the titled compound was
- 25 obtained. 1H NMR (500 MHz, CD_3OD) δ 4.48 (d, $J = 13$ Hz, 1 H); 4.41 (d, $J = 13$ Hz, 1 H); 4.41 (q, $J = 7$ Hz, 2 H); 4.07-4.04 (m, 1 H); 3.21 (m, 2 H); 3.08 (q, $J = 7$ Hz, 2 H); 2.45-2.34 (m, 3 H); 1.93-1.88 (m, 1H); 1.59 (s, 9 H); 1.41 (t, $J = 7$ Hz, 3 H); 1.16 (t, $J = 7$ Hz, 3 H). HRMS (ES) exact mass calcd for $C_{20}H_{31}N_3O_5$ ($M+H^+$): 394.2336. Found 394.2355.

30

EXAMPLE 80

diethyl 5-[[4-chlorophenyl]amino]methyl]-3-methyl-1H-pyrrole-2,4-dicarboxylate

5 Step A: diethyl 5-methyl-3-phenyl-1H-pyrrole-2,4-dicarboxylate

Following the procedures described in Example 1, Step C, but ethyl 3-oxobutanoate in place of tert-butyl 3-oxo-4-phenylbutanoate, the titled compound was obtained.

10 Step B: diethyl 5-formyl-3-methyl-1H-pyrrole-2,4-dicarboxylate

Following the procedures described in Example 1, Step D, but diethyl 5-methyl-3-phenyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-methyl-1H-pyrrole-2,4-dicarboxylate, the titled compound was obtained.

15 Step C: diethyl 5-[[4-chlorophenyl]amino]methyl]-3-methyl-1H-pyrrole-2,4-dicarboxylate

Following the procedures described in Example 1, Step E, but using diethyl 5-formyl-3-methyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate, the titled compound was
20 obtained.

Elemental analysis calculated for C₁₈H₂₁ClN₂O₄ :

C: 58.6; H: 5.78; N: 7.57

Found: C: 58.54; H: 5.42; N: 7.45

25

EXAMPLE 81

N-benzyl[3,5-bis(ethoxycarbonyl)-4-methyl-1H-pyrrol-2-yl]methanaminium chloride

Following the procedures described in Example 1, Step E, but using diethyl 5-formyl-3-methyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 1-phenylmethanamine in
30

place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for $C_{19}H_{24}N_2O_4$ ($M+H^+$): 345.1809. Found 345.1802.

EXAMPLE 82

5

[3,5-bis(ethoxycarbonyl)-4-methyl-1H-pyrrol-2-yl]-N-(pyridin-2-ylmethyl)
methanaminium chloride

Following the procedures described in Example 1, Step E, but using diethyl 5-formyl-3-methyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 1-pyridin-2-ylmethanamine in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for $C_{18}H_{24}ClN_3O_4$ ($M+H^+$): 346.1762. Found 346.1772.

EXAMPLE 83

15

[3,5-bis(ethoxycarbonyl)-4-methyl-1H-pyrrol-2-yl]-N-(2-chlorobenzyl)
methanaminium chloride

Following the procedures described in Example 1, Step E, but using diethyl 5-formyl-3-methyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 1-(2-chlorophenyl) methanamine in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for $C_{19}H_{23}ClN_2O_4$ ($M+H^+$): 379.1419. Found 379.1448.

EXAMPLE 84

25

[3,5-bis(ethoxycarbonyl)-4-methyl-1H-pyrrol-2-yl]-N-(3-chlorobenzyl)
methanaminium chloride

Following the procedures described in Example 1, Step E, but using diethyl 5-formyl-3-methyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 1-(3-chlorophenyl)

methanamine in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for $C_{19}H_{23}ClN_2O_4$ ($M+H^+$): 379.1419. Found 379.1444.

EXAMPLE 85

5

[3,5-bis(ethoxycarbonyl)-4-isopropyl-1H-pyrrol-2-yl]-N-(pyridin-2-ylmethyl)
methanaminium chloride

Step A: diethyl 3-isopropyl-5-methyl-1H-pyrrole-2,4-dicarboxylate

10

Following the procedures described in Example 1, Step C, but using ethyl 4-methyl-3-oxopentanoate in place of tert-butyl 3-oxo-4-phenylbutanoate, the titled compound was obtained.

Step B: diethyl 5-formyl-3-isopropyl-1H-pyrrole-2,4-dicarboxylate

15

Following the procedures described in Example 1, Step D, but using diethyl 3-isopropyl-5-methyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-methyl-1H-pyrrole-2,4-dicarboxylate, the titled compound was obtained.

20 Step C: [3,5-bis(ethoxycarbonyl)-4-isopropyl-1H-pyrrol-2-yl]-N-(pyridin-2-ylmethyl)methanaminium chloride

Following the procedures described in Example 1, Step E, but using diethyl 5-formyl-3-isopropyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 1-pyridin-2-ylmethanamine in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for $C_{20}H_{27}N_3O_4$ ($M+H^+$): 374.2075. Found 374.2088.

EXAMPLE 86

[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-(pyridin-2-ylmethyl)methanaminium chloride

- 5 Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 1-pyridin-2-ylmethanamine in place of 4-chloroaniline, the titled compound was obtained. ¹H NMR (500 MHz, CD₃OD) δ 8.71 (br d, J = 4 Hz, 1 H); 8.07 (dt, J = 8, 2 Hz, 1 H); 7.67 (d, J = 8 Hz, 1 H); 7.60 (dd, J = 7, 5 Hz, 1 H); 4.57 (s, 2H); 4.50 (s, 2H); 4.38 (q, J = 7 Hz, 2H); 3.06 (q, J = 7 Hz, 2 H); 1.59 (s, 9H); 1.40 (t, J = 7 Hz, 3H); 1.13 (t, J = 7 Hz, 3 H). HRMS (ES) exact mass calcd for C₂₁H₂₉N₃O₄ (M+H⁺): 388.2231. Found 388.2247.

15 EXAMPLE 87

N-{[3-[(benzyloxy)carbonyl]-5-(tert-butoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-4-methoxybenzenaminium trifluoroacetate

- 20 Step A: 5-(1-hydroxypropylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione
 Following the procedures described in Example 1, Step A, but using propanoyl chloride in place of phenylacetyl chloride, the titled compound was obtained.
- 25 Step B: tert-butyl 3-oxopentanoate
 Following the procedures described in Example 1, Step B, but using 5-(1-hydroxypropylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione in place of 5-(1-hydroxy-2-phenylethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione, the titled compound was obtained
- 30 .

Step C: 4-benzyl 2-tert-butyl 3-ethyl-5-methyl-1H-pyrrole-2,4-dicarboxylate

Following the procedures described in Example 1, Step C, but using tert-butyl 3-oxopentanoate in place of tert-butyl 3-oxo-4-phenylbutanoate and benzyl 3-oxobutanoate in place of ethyl 3-oxobutanoate, the titled compound was obtained.

5

Step D: 4-benzyl 2-tert-butyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate

Following the procedures described in Example 1, Step D, but 4-benzyl 2-tert-butyl 3-ethyl-5-methyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-methyl-1H-pyrrole-2,4-dicarboxylate, the titled compound was obtained.

10

Step E: N-([3-[(benzyloxy)carbonyl]-5-(tert-butoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl)-4-methoxybenzenaminium trifluoroacetate

Following the procedures described in Example 1, Step E, but using 4-benzyl-2-tert-butyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl-3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and 4-methoxyaniline in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₇H₃₂N₂O₅ (M+H⁺): 465.2384. Found 465.2385.

15

20

EXAMPLE 88

N-([5-(tert-butoxycarbonyl)-3-carboxy-4-ethyl-1H-pyrrol-2-yl]methyl)-4-methoxybenzenaminium trifluoroacetate

A suspension of N-([3-[(benzyloxy)carbonyl]-5-(tert-butoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl)-4-methoxybenzenaminium trifluoroacetate (1.04 mmol) and 10% Pd-C (11mg, 0.10 mmol) in EtOH (3ml) was placed under a H₂ balloon. The reaction was stirred at room temperature for 2 hours. The balloon was then removed and the reaction mixture was purged with argon. The mixture was filtered through celite and rinsed thoroughly with EtOH. 30mg of the crude reaction

25

product was purified by reverse phase HPLC to give a white solid. HRMS (ES) exact mass calcd for C₂₀H₂₆N₂O₅ (M+H⁺): 375.1915. Found 375.1918.

EXAMPLE 89

5

N-[(5-(tert-butoxycarbonyl)-4-ethyl-3-[(2-hydroxyethyl)amino]carbonyl)-1H-pyrrol-2-yl)methyl]-4-methoxybenzenaminium trifluoroacetate

A solution of N-{[5-(tert-butoxycarbonyl)-3-carboxy-4-ethyl-1H-pyrrol-2-yl]methyl}-4-methoxybenzenaminium trifluoroacetate (0.12 mmol) in 1ml of
10 DMF was treated with 2-aminoethanol (10 ml, 0.14 mmol), DIEA (0.100 ml, 0.59 mmol), and HOBT (31.9 mg, 0.24 mmol). EDC (24.9 mg, 0.13 mmol) was then added and the reaction mixture stirred at room temperature overnight. The reaction was purified by reverse phase HPLC to give a white powder. HRMS (ES) exact mass calcd for C₂₂H₃₁N₃O₅ (M+H⁺): 418.2336. Found 418.2337.

15

EXAMPLE 90

N-({5-(tert-butoxycarbonyl)-4-ethyl-3-[(ethylamino)carbonyl]-1H-pyrrol-2-yl}methyl)-4-methoxybenzenaminium trifluoroacetate

20

Following the procedures described in Example 120, but using ethanamine in place of 2-aminoethanol, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₂H₃₁N₃O₄ (M+H⁺): 402.2387. Found 402.2382.

EXAMPLE 91

25

2-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-[(4-methoxyphenyl)ammonio]methyl)-1H-pyrrol-3-yl]carbonyl}amino)methylpyridinium bis(trifluoroacetate)

Following the procedures described in Example 120, but using 1-pyridin-2-ylmethanamine in place of 2-aminoethanol, the titled compound was
30 obtained. ¹H NMR (500 MHz, CD₃OD) δ 8.60 (br d, J = 5 Hz, 1 H); 8.06 (t, J = 9

Hz, 1 H); 7.66 (d, J = 6 Hz, 1 H); 7.53 (m, 1 H); 7.23 (d, J = 9 Hz, 2 H); 7.00 (d, J = 9 Hz, 2 H); 4.82 (s, 2 H); 4.58 (s, 2 H); 3.81 (s, 3 H); 3.10 (q, J = 7 Hz, 2 H); 1.57 (s, 9 H); 1.20 (t, J = 7 Hz, 3 H). HRMS (ES) exact mass calcd for C₂₆H₃₂N₄O₄ (M+H⁺): 465.2496. Found 465.2497.

5

EXAMPLE 92

4-([5-(tert-butoxycarbonyl)-4-ethyl-2-[(4-methoxyphenyl)ammonio]methyl]-1H-pyrrol-3-yl)carbonylamino)methyl]pyridinium bis(trifluoroacetate)

10 Following the procedures described in Example 120, but using 1-pyridin-4-ylmethanamine in place of 2-aminoethanol, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₆H₃₂N₄O₄ (M+H⁺): 465.2496. Found 465.2494.

15

EXAMPLE 93

N-([5-(tert-butoxycarbonyl)-4-ethyl-3-[(propylamino)carbonyl]-1H-pyrrol-2-yl)methyl]-4-methoxybenzenaminium trifluoroacetate

20 Following the procedures described in Example 120, but using propan-1-amine in place of 2-aminoethanol, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₃H₃₃N₃O₄ (M+H⁺): 416.2544. Found 416.2550.

EXAMPLE 94

25 N-([5-(tert-butoxycarbonyl)-4-ethyl-3-([5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl]amino)carbonyl)-1H-pyrrol-2-yl)methyl]-4-methoxybenzenaminium trifluoroacetate

30 A solution of N-([5-(tert-butoxycarbonyl)-3-carboxy-4-ethyl-1H-pyrrol-2-yl)methyl]-4-methoxybenzenaminium trifluoroacetate (0.107 mmol) in 1ml of DMF was treated with 5-(aminomethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (31.8

mg, 0.32 mmol), DIEA (0.09 ml, 0.54 mmol), and HOAT (29.1 mg, 0.21 mmol). EDC (22.6 mg, 0.12 mmol) was then added and the reaction mixture stirred at room temperature overnight. The reaction was purified by reverse phase HPLC to give a white solid. HRMS (ES) exact mass calcd for C₂₃H₃₀N₆O₅ (M+H⁺): 471.2350.

5 Found 471.2337.

EXAMPLE 95

2-(2-{{(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-
10 1H-pyrrol-3-yl)carbonyl}amino}ethyl)pyridinium bis(trifluoroacetate)

Following the procedures described in Example 94, but using 2-pyridin-2-ylethanamine in place of 5-(aminomethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₇H₃₄N₄O₄ (M+H⁺): 479.2653. Found 479.2672.

15

EXAMPLE 96

2-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-
20 1H-pyrrol-3-yl)carbonyl}amino}methyl)-1H-imidazol-1-ium bis(trifluoroacetate)

Following the procedures described in Example 94, but using 1-(1H-imidazol-2-yl)methanamine in place of 5-(aminomethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₄H₃₁N₅O₄ (M+H⁺): 454.2449. Found 454.2405.

25

EXAMPLE 97

N-{{[5-(tert-butoxycarbonyl)-4-ethyl-3-{{(5-oxopyrrolidin-2-yl)methyl}amino}
carbonyl]-1H-pyrrol-2-yl}methyl}-4-methoxybenzenaminium trifluoroacetate

Following the procedures described in Example 94, but using
30 5-(aminomethyl)pyrrolidin-2-one in place of 5-(aminomethyl)-2,4-dihydro-3H-1,2,4-

triazol-3-one, the titled compound was obtained. HRMS (ES) exact mass calcd for $C_{25}H_{34}N_4O_5$ ($M+H^+$): 471.2592. Found 471.2602.

EXAMPLE 98

5

3-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl})-1H-pyrrol-3-yl)carbonyl]amino}methyl)pyridinium bis(trifluoroacetate)

Following the procedures described in Example 94, but using 1-pyridin-3-ylmethanamine in place of 5-(aminomethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one, the titled compound was obtained. HRMS (ES) exact mass calcd for $C_{26}H_{32}N_4O_4$ ($M+H^+$): 465.2487. Found 465.2497.

EXAMPLE 99

15 2-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl})-1H-pyrrol-3-yl)carbonyl]amino}methyl)-3H-benzimidazol-1-ium bis(trifluoroacetate)

Following the procedures described in Example 94, but using 1-(1H-benzimidazol-2-yl)methanamine in place of 5-(aminomethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one, the titled compound was obtained. HRMS (ES) exact mass calcd for $C_{28}H_{33}N_5O_4$ ($M+H^+$): 504.2606. Found 504.2600.

EXAMPLE 100

25 N-[(5-(tert-butoxycarbonyl)-4-ethyl-3-{{(isoxazol-3-ylmethyl)amino}carbonyl})-1H-pyrrol-2-yl)methyl]-4-methoxybenzenaminium trifluoroacetate

Following the procedures described in Example 94, but using 1-isoxazol-3-ylmethanamine in place of 5-(aminomethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one, the titled compound was obtained. HRMS (ES) exact mass calcd for $C_{24}H_{30}N_4O_5$ ($M+H^+$): 455.2289. Found 455.2281.

30

EXAMPLE 101

N-{[3-([2-(acetylamino)ethyl]amino)carbonyl]-5-(tert-butoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-4-methoxybenzenaminium trifluoroacetate

- 5 Following the procedures described in Example 94, but using N-(2-aminoethyl)acetamide in place of 5-(aminomethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₄H₃₄N₄O₅ (M+H⁺): 459.2602. Found 459.2590.

10

EXAMPLE 102

N-{[5-(tert-butoxycarbonyl)-4-ethyl-3-([[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]amino)carbonyl]-1H-pyrrol-2-yl]methyl}-4-methoxybenzenaminium trifluoroacetate

- 15 Following the procedures described in Example 94, but using (5-methyl-1,3,4-oxadiazol-2-yl)methylamine in place of 5-(aminomethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₄H₃₁N₅O₅ (M+H⁺): 470.2398. Found 470.2381.

EXAMPLE 103

20

N-{[5-(tert-butoxycarbonyl)-4-ethyl-3-([2-sulfoethyl]amino)carbonyl]-1H-pyrrol-2-yl]methyl}-4-methoxybenzenaminium trifluoroacetate

- 25 Following the procedures described in Example 94, but using 2-aminoethanesulfonic acid in place of 5-(aminomethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₂H₃₁N₃O₇S (M+H⁺): 482.1956. Found 482.1956.

EXAMPLE 104

N-{[3-[(benzylamino)carbonyl]-5-(tert-butoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]
methyl]-4-methoxybenzenaminium trifluoroacetate

- 5 Following the procedures described in Example 120, but using
1-phenylmethanamine in place of 2-aminoethanol, the titled compound was obtained.
HRMS (ES) exact mass calcd for C₂₇H₃₃N₃O₄ (M+H⁺): 464.2544. Found 464.2545.

EXAMPLE 105

10

3-(2-{{{(5-(tert-butoxycarbonyl)-4-ethyl-2-[[4-methoxyphenyl]ammonio]methyl)-
1H-pyrrol-3-yl)carbonyl}amino}ethyl)-5-methyl-4H-1,2,4-triazol-4-ium
bis(trifluoroacetate)

- 15 Following the procedures described in Example 94, but using
2-(5-methyl-4H-1,2,4-triazol-3-yl)ethanamine in place of 2-aminoethanol, the titled
compound was obtained. HRMS (ES) exact mass calcd for C₂₅H₃₄N₆O₄ (M+H⁺):
483.2715. Found 483.2687.

EXAMPLE 106

20

4-(((5-(tert-butoxycarbonyl)-4-ethyl-2-[[4-methoxyphenyl]ammonio]methyl)-1H-
pyrrol-3-yl)carbonyl)amino)methyl)-2-methyl-1,3-thiazol-3-ium bis(trifluoroacetate)

- 25 Following the procedures described in Example 94, but using
(2-methyl-1,3-thiazol-4-yl)methylamine in place of 2-aminoethanol, the titled
compound was obtained. HRMS (ES) exact mass calcd for C₂₅H₃₂N₄O₄S
(M+H⁺): 485.2217. Found 485.2201.

EXAMPLE 107

4-(2-([(5-(tert-butoxycarbonyl)-4-ethyl-2-([(4-methoxyphenyl)ammonio]methyl)-
1H-pyrrol-3-yl)carbonyl]amino)ethyl)-1H-pyrazol-1-ium bis(trifluoroacetate)

- 5 Following the procedures described in Example 94, but using
2-(1H-pyrazol-4-yl)ethanamine in place of 2-aminoethanol, the titled compound was
obtained. HRMS (ES) exact mass calcd for C₂₅H₃₃N₅O₄ (M+H⁺): 468.2606.
Found 468.2610.

10 EXAMPLE 108

N-[(5-(tert-butoxycarbonyl)-4-ethyl-3-([(1H-indol-6-ylmethyl)amino]carbonyl)-1H-
pyrrol-2-yl)methyl]-4-methoxybenzenaminium trifluoroacetate

- 15 Following the procedures described in Example 94, but using
1-(1H-indol-6-yl)methanamine in place of 2-aminoethanol, the titled compound was
obtained. HRMS (ES) exact mass calcd for C₂₉H₃₄N₄O₄ (M+H⁺): 503.2653.
Found 503.2653.

EXAMPLE 109

- 20 6-([(5-(tert-butoxycarbonyl)-4-ethyl-2-([(4-methoxyphenyl)ammonio]methyl)-1H-
pyrrol-3-yl)carbonyl]amino)methyl)-2-methylimidazo[2,1-b][1,3]thiazol-7-ium
bis(trifluoroacetate)
-

- 25 Following the procedures described in Example 94, but using
(2-methylimidazo[2,1-b][1,3]thiazol-6-yl)methylamine in place of 2-aminoethanol,
the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₇H₃₃N₅O₄S
(M+H⁺): 524.2326. Found 524.2300.

EXAMPLE 110

5-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-1H-pyrrol-3-yl)carbonyl]amino}methyl)-3-methyl-4H-1,2,4-triazole-1,4-dium
5 tris(trifluoroacetate)

Following the procedures described in Example 94, but using (5-methyl-4H-1,2,4-triazol-3-yl)methylamine in place of 2-aminoethanol, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₄H₃₂N₆O₄ (M+H⁺): 469.2558. Found 469.2511.

10

EXAMPLE 111

4-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-1H-pyrrol-3-yl)carbonyl]amino}methyl)-1-methyl-1H-pyrazol-2-ium bis(trifluoroacetate)

15 Following the procedures described in Example 94, but using (1-methyl-1H-pyrazol-4-yl)methylamine in place of 2-aminoethanol, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₅H₃₃N₅O₄ (M+H⁺): 468.2606. Found 468.2598.

20

EXAMPLE 112

N-{{[5-(tert-butoxycarbonyl)-4-ethyl-3-{{(1-methyl-5-oxopyrrolidin-2-yl)methyl}amino}carbonyl]-1H-pyrrol-2-yl]methyl}-4-methoxybenzenaminium trifluoroacetate

25 Following the procedures described in Example 94, but using 5-(aminomethyl)-1-methylpyrrolidin-2-one in place of 2-aminoethanol, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₆H₃₆N₄O₅ (M+H⁺): 485.2759. Found 485.2752

EXAMPLE 113

2-(2-{{(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-
1H-pyrrol-3-yl)carbonyl}amino}ethyl)-5-methoxy-3H-benzimidazol-1-ium
5 bis(trifluoroacetate)

Following the procedures described in Example 94, but using
2-(6-methoxy-1H-benzimidazol-2-yl)ethanamine in place of 2-aminoethanol, the
titled compound was obtained. HRMS (ES) exact mass calcd for C₃₀H₃₇N₅O₅
(M+H⁺): 548.2868. Found 548.2868.

10

EXAMPLE 114

5-(2-{{(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-
1H-pyrrol-3-yl)carbonyl}amino}ethyl)-1H-1,2,4-triazol-1-ium bis(trifluoroacetate)

15 Following the procedures described in Example 94, but using
2-(1H-1,2,4-triazol-5-yl)ethanamine in place of 2-aminoethanol, the titled compound
was obtained. HRMS (ES) exact mass calcd for C₂₄H₃₂N₆O₄ (M+H⁺): 469.2558.
Found 469.2542.

20

EXAMPLE 115

2-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}
methyl}-1H-pyrrol-3-yl)carbonyl}amino}methyl)-1-methyl-1H-imidazol-
3-ium bis(trifluoroacetate)

25 Following the procedures described in Example 94, but using
(1-methyl-1H-imidazol-2-yl)methylamine in place of 2-aminoethanol, the titled
compound was obtained. HRMS (ES) exact mass calcd for C₂₅H₃₃N₅O₄
(M+H⁺): 468.2606. Found 468.2610.

EXAMPLE 116

6-(((5-(tert-butoxycarbonyl)-4-ethyl-2-(((4-methoxyphenyl)ammonio)methyl)-
1H-pyrrol-3-yl)carbonyl]amino)methyl)-2,3-dihydroimidazo[2,1-b][1,3]thiazol-
5 4-ium bis(trifluoroacetate)

Following the procedures described in Example 94, but using
(1-methyl-1H-imidazol-2-yl)methylamine in place of 2-aminoethanol, the titled
compound was obtained. HRMS (ES) exact mass calcd for C₂₆H₃₃N₅O₄S
(M+H⁺): 512.2326. Found 512.2278.

10

EXAMPLE 117

2-(((5-(tert-butoxycarbonyl)-4-ethyl-2-(((4-methoxyphenyl)ammonio)
methyl)-1H-pyrrol-3-yl)carbonyl]amino)methyl)-4-methyl-1H-imidazol-
15 3-ium bis(trifluoroacetate)

Following the procedures described in Example 94, but using
(4-methyl-1H-imidazol-2-yl)methylamine in place of 2-aminoethanol, the titled
compound was obtained. HRMS (ES) exact mass calcd for C₂₅H₃₃N₅O₄
(M+H⁺): 468.2606. Found 468.2589.

20

EXAMPLE 118

2-(((5-(tert-butoxycarbonyl)-4-ethyl-2-(((4-methoxyphenyl)ammonio)methyl)-
1H-pyrrol-3-yl)carbonyl]amino)methyl)-8-methylimidazo[1,2-a]pyridin-4-ium
25 bis(trifluoroacetate)

Following the procedures described in Example 94, but using
(8-methylimidazo[1,2-a]pyridin-2-yl)methylamine in place of 2-aminoethanol, the
titled compound was obtained. HRMS (ES) exact mass calcd for C₂₉H₃₅N₅O₄
(M+H⁺): 518.2762. Found 518.2747.

30

EXAMPLE 119

3-(1-{[(5-(tert-butoxycarbonyl)-4-ethyl-2-{[(4-methoxyphenyl)ammonio]
methyl}-1H-pyrrol-3-yl)carbonyl]amino}ethyl)-5-methyl-4H-1,2,4-triazol-
5 4-ium bis(trifluoroacetate)

Following the procedures described in Example 94, but using
1-(5-methyl-4H-1,2,4-triazol-3-yl)ethanamine in place of 2-aminoethanol, the titled
compound was obtained. HRMS (ES) exact mass calcd for C₂₅H₃₄N₆O₄ (M+H⁺):
483.2715. Found 483.2720.

10

EXAMPLE 120

2-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-{[(4-methoxyphenyl)ammonio]methyl}-
1H-pyrrol-3-yl)carbonyl]amino}methyl)quinolinium bis(trifluoroacetate)

15 Following the procedures described in Example 94, but using
1-quinolin-2-ylmethanamine in place of 2-aminoethanol, the titled compound was
obtained. HRMS (ES) exact mass calcd for C₃₀H₃₄N₄O₄ (M+H⁺): 515.2653.
Found 515.2617.

20

EXAMPLE 121

2-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-{[(4-methoxyphenyl)ammonio]methyl}-
1H-pyrrol-3-yl)carbonyl]amino}methyl)-6-methylpyridinium bis(trifluoroacetate)

Following the procedures described in Example 94, but using
25 (6-methylpyridin-2-yl)methylamine in place of 2-aminoethanol, the titled compound
was obtained. HRMS (ES) exact mass calcd for C₂₇H₃₄N₄O₄ (M+H⁺): 479.2553.
Found 479.2627.

EXAMPLE 122

N-([5-(tert-butoxycarbonyl)-4-ethyl-3-([(4-methyl-1,3-thiazol-2-yl)methyl]amino)carbonyl]-1H-pyrrol-2-yl)methyl]-4-methoxybenzenaminium trifluoroacetate

- 5 Following the procedures described in Example 94, but using (4-methyl-1,3-thiazol-2-yl)methylamine in place of 2-aminoethanol, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₅H₃₂N₄O₄S (M+H⁺): 485.2217. Found 485.2215.

10 EXAMPLE 123

3-([(5-(tert-butoxycarbonyl)-4-ethyl-2-([(4-methoxyphenyl)ammonio]methyl)-1H-pyrrol-3-yl)carbonyl]amino)methyl)-6,7-dihydro-5H-cyclopenta[b]pyridinium bis(trifluoroacetate)

- 15 Following the procedures described in Example 94, but using 1-(6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl)methanamine in place of 2-aminoethanol, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₉H₃₆N₄O₄ (M+H⁺): 505.2810. Found 505.2807.

20 EXAMPLE 124

3-([(5-(tert-butoxycarbonyl)-4-ethyl-2-([(4-methoxyphenyl)ammonio]methyl)-1H-pyrrol-3-yl)carbonyl]amino)methyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridinium bis(trifluoroacetate)

- 25 Following the procedures described in Example 94, but using 1-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-3-yl)methanamine in place of 2-aminoethanol, the titled compound was obtained. HRMS (ES) exact mass calcd for C₃₁H₄₀N₄O₄ (M+H⁺): 533.3123. Found: 533.3108.

EXAMPLE 125

N-([5-(tert-butoxycarbonyl)-4-ethyl-3-([2-(4-methyl-1,3-thiazol-5-yl)ethyl]amino)carbonyl]-1H-pyrrol-2-yl)methyl]-4-methoxybenzenaminium trifluoroacetate

- 5 Following the procedures described in Example 94, but using 2-(4-methyl-1,3-thiazol-5-yl)ethanamine in place of 2-aminoethanol, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₆H₃₄N₄O₄S (M+H⁺): 499.2374. Found 499.2408.

10 EXAMPLE 126

3-([5-(tert-butoxycarbonyl)-4-ethyl-2-([(4-methoxyphenyl)ammonio]methyl)-1H-pyrrol-3-yl)carbonyl]amino)methyl]-1-methylpiperidinium bis(trifluoroacetate)

- 15 Following the procedures described in Example 94, but using (1-methylpiperidin-3-yl)methylamine in place of 2-aminoethanol, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₇H₄₀N₄O₄ (M+H⁺): 485.3123. Found 485.3099.

EXAMPLE 127

- 20 4-(2-([5-(tert-butoxycarbonyl)-4-ethyl-2-([(4-methoxyphenyl)ammonio]methyl)-1H-pyrrol-3-yl)carbonyl]amino)-1-pyridinium-4-ylethyl)morpholin-4-ium tris(trifluoroacetate)

- 25 Following the procedures described in Example 94, but using 2-morpholin-4-yl-2-pyridin-4-ylethanamine in place of 2-aminoethanol, the titled compound was obtained. HRMS (ES) exact mass calcd for C₃₁H₄₁N₅O₅ (M+H⁺): 564.3181. Found 564.3199.

EXAMPLE 128

4-(2-{[(5-(tert-butoxycarbonyl)-4-ethyl-2-{[(4-methoxyphenyl)ammonio]
methyl]-1H-pyrrol-3-yl)carbonyl]amino}-1-pyridinium-3-ylethyl)morpholin-
5 4-ium tris(trifluoroacetate)

Following the procedures described in Example 94, but using
2-morpholin-4-yl-2-pyridin-3-ylethanamine in place of 2-aminoethanol, the titled
compound was obtained. HRMS (ES) exact mass calcd for C₃₁H₄₁N₅O₅ (M+H⁺):
564.3181. Found 564.3167.

10

EXAMPLE 129

N-{[(5-(tert-butoxycarbonyl)-4-ethyl-3-({[(5-fluoro-2-oxo-2,3-dihydro-1H-indol-3-yl)
methyl]amino}carbonyl)-1H-pyrrol-2-yl)methyl]-4-methoxybenzenaminium
15 trifluoroacetate

Following the procedures described in Example 94, but using
3-(aminomethyl)-5-fluoro-1,3-dihydro-2H-indol-2-one in place of 2-aminoethanol,
the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₉H₃₃FN₄O₅
(M+H⁺): 537.2508. Found 537.2512.

20

EXAMPLE 130

3-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-{[(4-methoxyphenyl)ammonio]methyl]-
1H-pyrrol-3-yl)carbonyl]amino}methyl)-5-cyclopropyl-1H-pyrazol-1-ium
25 bis(trifluoroacetate)

Following the procedures described in Example 94, but using
(5-cyclopropyl-1H-pyrazol-3-yl)methylamine in place of 2-aminoethanol, the titled
compound was obtained. HRMS (ES) exact mass calcd for C₂₇H₃₅N₅O₄ (M+H⁺):
494.2762. Found 494.2757.

30

EXAMPLE 131

2-([5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl)
 (hydroxy)ammonio]methyl]pyridinium bis(trifluoroacetate)

- 5 To a solution of 2-tert-butyl 4-ethyl 3-ethyl-5-([(E)-oxido(pyridin-2-ylmethylene)amino]methyl)-1H-pyrrole-2,4-dicarboxylate in 5 ml MeOH was added solid NaBH₄ (170 mg, 4.48 mmol). The reaction stirred at room temperature for 30 minutes and was then quenched by adding 1N HCl. The mixture was poured into a separatory funnel containing saturated NaHCO₃ and extracted with EtOAc (3x).
- 10 The combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The reaction was purified by normal phase chromatography using 0-4% MeOH in CH₂Cl₂ to give a white solid. HRMS (ES) exact mass calcd for C₂₁H₂₉N₃O₅ (M+H⁺): 404.2180. Found 404.2174.

15 EXAMPLE 132

2-([5-(tert-butoxycarbonyl)-4-ethyl-2-([(4-methoxyphenyl)ammonio]methyl)-1H-pyrrol-3-yl]carbonyl]oxy]methyl]pyridinium bis(trifluoroacetate)

- A solution of N-[5-(tert-butoxycarbonyl)-3-carboxy-4-ethyl-1H-pyrrol-2-yl]methyl]-4-methoxyaniline (0.53 mmol) was dissolved in dry THF (800
- 20 ul). Pyridin-2-ylmethanol (10ul, 0.05mmol) and triphenylphosphine (21.7 mg, 0.08 mmol) were added to the solution, followed by DEAD (10ul, 0.05 mmol). The reaction stirred at room temperature for 1.5 hours and then concentrated *in vacuo*. The residue was dissolved in acetonitrile and purified by reverse phase chromatography to give a white solid. HRMS (ES) exact mass calcd for C₂₆H₃₁N₃O₅
- 25 (M+H⁺): 466.2337. Found 466.2346.

EXAMPLE 133

N-{{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-(2-phenylethyl)-1H-pyrrol-2-yl]
methyl}-4-chlorobenzenaminium trifluoroacetate

5

Step A: 5-(1-hydroxy-3-phenylpropylidene)-2,2-dimethyl-1,3-dioxane-4,6-
dione

Following the procedures described in Example 1, Step A, but using 3-phenylpropanoyl chloride in place of phenylacetyl chloride, the titled compound was
10 obtained.

Step B: tert-butyl 3-oxo-5-phenylpentanoate

Following the procedures described in Example 1, Step B, but using
5-(1-hydroxy-3-phenylpropylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione in place of
15 5-(1-hydroxy-2-phenylethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione, the titled
compound was obtained.

Step C: 2-tert-butyl 4-ethyl 5-methyl-3-(2-phenylethyl)-1H-pyrrole-2,4-
Dicarboxylate

20 Following the procedures described in Example 1, Step C, but using
tert-butyl 3-oxo-5-phenylpentanoate in place of tert-butyl 3-oxo-4-phenylbutanoate,
the titled compound was obtained.

Step D: 2-tert-butyl 4-ethyl 5-formyl-3-(2-phenylethyl)-1H-pyrrole-2,4-
Dicarboxylate

25

Following the procedures described in Example 1, Step D, but using
2-tert-butyl 4-ethyl 5-methyl-3-(2-phenylethyl)-1H-pyrrole-2,4-dicarboxylate in place
of 2-tert-butyl 4-ethyl 3-benzyl-5-methyl-1H-pyrrole-2,4-dicarboxylate, the titled
compound was obtained.

30

Step E: N-([5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-(2-phenylethyl)-1H-pyrrol-2-yl)methyl]-4-chlorobenzenaminium trifluoroacetate

Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 5-formyl-3-(2-phenylethyl)-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₇H₃₁ClN₂O₄ (M+H⁺): 483.2045. Found 483.2064.

EXAMPLE 134

10

2-amino-N-([5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl)methyl]glycinamide trifluoroacetate

Following the procedures described in Example 1, Step E, but using 2-tert-butyl 4-ethyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate in place of 2-tert-butyl 4-ethyl 3-benzyl-5-formyl-1H-pyrrole-2,4-dicarboxylate and glycine in place of 4-chloroaniline, the titled compound was obtained. HRMS (ES) exact mass calcd for C₁₇H₂₇N₃O₅ (M+H⁺): 354.2024. Found 354.2040.

EXAMPLE 135

20

N-([5-(tert-butoxycarbonyl)-4-ethyl-3-glycinamide-1H-pyrrol-2-yl)methyl]-4-methoxybenzenaminium trifluoroacetate

Following the procedures described in Example 97, but using glycine in place of 5-(aminomethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one, the titled compound was obtained. HRMS (ES) exact mass calcd for C₂₂H₃₀N₄O₅ (M+H⁺): 431.2289. Found 431.2282.

30

EXAMPLE 136

The salt compounds prepared above may be neutralized using techniques known in the art. For example, the salt may be treated with a suitable dilute aqueous base solution such as dilute aqueous NaOH, potassium carbonate, ammonia and sodium bicarbonate to produce the free form, or non-salt form, of the compound.

5 Listed below is the free form name for corresponding salt compound described in the example recited:

Example	Free form name
2	2-tert-butyl 4-ethyl 3-ethyl-5-({[(5-oxopyrrolidin-2-yl)methyl]amino}methyl)-1H-pyrrole-2,4-dicarboxylate
3	2-tert-butyl 4-ethyl 3-ethyl-5-({[(1H-indol-2-ylmethyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate
4	2-tert-butyl 4-ethyl 5-({[(3,4-dichlorophenyl)amino]methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate
5	2-tert-butyl 4-ethyl 3-ethyl-5-({[(4-methylphenyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate
6	2-tert-butyl 4-ethyl 3-ethyl-5-({[(4-hydroxyphenyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate
7	2-tert-butyl 4-ethyl 3-ethyl-5-({[(4-methoxyphenyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate
8	2-tert-butyl 4-ethyl 5-({[(4-chlorophenyl)(methyl)amino]methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate
9	2-tert-butyl 4-ethyl 3-ethyl-5-({[(6-methylpyridin-2-yl)methyl]amino}methyl)-1H-pyrrole-2,4-dicarboxylate
10	2-tert-butyl 4-ethyl 5-({[(5-cyclopropyl-1H-pyrazol-3-yl)methyl]amino}methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate
11	2-tert-butyl 4-ethyl 5-({[(3,5-dimethyl-1H-pyrazol-4-yl)methyl]amino}methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate

12	2-tert-butyl 4-ethyl 3-ethyl-5-([(1H-indol-2-ylmethyl)amino]methyl)-1H-pyrrole-2,4-dicarboxylate
13	2-tert-butyl 4-ethyl 3-ethyl-5-([(1H-imidazol-2-ylmethyl)amino]methyl)-1H-pyrrole-2,4-dicarboxylate
14	2-tert-butyl 4-ethyl 3-ethyl-5-([(5-methyl-4H-1,2,4-triazol-3-yl)methyl]amino)methyl)-1H-pyrrole-2,4-dicarboxylate
15	2-tert-butyl 4-ethyl 3-ethyl-5-([(2-methylimidazo[2,1-b][1,3]thiazol-6-yl)methyl]amino)methyl)-1H-pyrrole-2,4-dicarboxylate
16	2-tert-butyl 4-ethyl 3-ethyl-5-([(4-methyl-1H-imidazol-2-yl)methyl]amino)methyl)-1H-pyrrole-2,4-dicarboxylate
17	2-tert-butyl 4-ethyl 3-ethyl-5-([(1-methyl-1H-imidazol-2-yl)methyl]amino)methyl)-1H-pyrrole-2,4-dicarboxylate
18	2-tert-butyl 4-ethyl 3-ethyl-5-([(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl]amino)methyl)-1H-pyrrole-2,4-dicarboxylate
19	2-tert-butyl 4-ethyl 3-ethyl-5-([(1H-1,2,4-triazol-5-ylmethyl)amino]methyl)-1H-pyrrole-2,4-dicarboxylate
20	2-tert-butyl 4-ethyl 3-ethyl-5-([(imidazo[2,1-b][1,3]thiazol-6-ylmethyl)amino]methyl)-1H-pyrrole-2,4-dicarboxylate
21	2-tert-butyl 4-ethyl 5-([(6-chloro-1H-benzimidazol-2-yl)methyl]amino)methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate
22	2-tert-butyl 4-ethyl 3-ethyl-5-([(4-oxo-3,4-dihydrophthalazin-1-yl)methyl]amino)methyl)-1H-pyrrole-2,4-dicarboxylate
23	2-tert-butyl 4-ethyl 3-ethyl-5-([(1H-indol-6-ylmethyl)amino]methyl)-1H-pyrrole-2,4-dicarboxylate
24	2-tert-butyl 4-ethyl 3-ethyl-5-([(4-methyl-1,3-thiazol-2-yl)methyl]amino)methyl)-1H-pyrrole-2,4-dicarboxylate
25	2-tert-butyl 4-ethyl 3-ethyl-5-([(8-methylimidazo[1,2-a]pyridin-2-yl)methyl]amino)methyl)-1H-pyrrole-2,4-dicarboxylate
26	2-tert-butyl 4-ethyl 5-([(1H-benzimidazol-2-ylmethyl)amino]methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate

27	2-tert-butyl 4-ethyl 3-ethyl-5-{[(3-methylphenyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate
28	2-tert-butyl 4-ethyl 3-ethyl-5-{[(4-isopropylphenyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate
29	2-tert-butyl 4-ethyl 3-ethyl-5-{[(4-ethylphenyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate
30	2-tert-butyl 4-ethyl 5-{[(3,5-dimethylphenyl)amino]methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate
31	2-tert-butyl 4-ethyl 5-{[(3,4-dimethoxyphenyl)amino]methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate
32	2-tert-butyl 4-ethyl 3-ethyl-5-{[(2-pyridin-2-ylethyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate
33	2-tert-butyl 4-ethyl 3-ethyl-5-({[(1-methyl-1H-pyrazol-4-yl)methyl]amino} methyl)-1H-pyrrole-2,4-dicarboxylate
34	2-tert-butyl 4-ethyl 5-{[(4-ethoxyphenyl)amino]methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate
35	2-tert-butyl 4-ethyl 5-{[(3,4-dimethylphenyl)amino]methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate
36	2-tert-butyl 4-ethyl 5-[(1,3-benzodioxol-5-ylamino)methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate
37	2-tert-butyl 4-ethyl 3-ethyl-5-{[(4-isopropoxyphenyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate
38	2-tert-butyl 4-ethyl 3-ethyl-5-{[(1,3-thiazol-4-ylmethyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate
39	2-tert-butyl 4-ethyl 3-ethyl-5-{[(1,3-thiazol-5-ylmethyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate
40	2-tert-butyl 4-ethyl 3-ethyl-5-{[(1,3-thiazol-2-ylmethyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate
41	2-tert-butyl 4-ethyl 3-ethyl-5-{[(isoxazol-5-ylmethyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate

42	2-tert-butyl 4-ethyl 5-({[(1,5-dimethyl-1H-pyrazol-4-yl)methyl]amino} methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate
43	2-tert-butyl 4-ethyl 5-{{[(4-tert-butylphenyl)amino]methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate
44	2-tert-butyl 4-ethyl 5-({[(4-(dimethylamino)phenyl)amino]methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate
45	2-tert-butyl 4-ethyl 3-ethyl-5-{{[(2-methylphenyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate
46	2-tert-butyl 4-ethyl 3-ethyl-5-{{[(2-methoxyphenyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate
47	2-tert-butyl 4-ethyl 3-ethyl-5-{{[(4-propylphenyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate
48	2-tert-butyl 4-ethyl 5-{{[(2,5-dimethoxyphenyl)amino]methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate
49	2-tert-butyl 4-ethyl 5-{{[(4-butylphenyl)amino]methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate
50	2-tert-butyl 4-ethyl 3-ethyl-5-{{[(3-hydroxy-4-methoxyphenyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate
51	2-tert-butyl 4-ethyl 3-ethyl-5-[(1H-indol-4-ylamino)methyl]-1H-pyrrole-2,4-dicarboxylate
52	2-tert-butyl 4-ethyl 3-ethyl-5-[(1H-indol-6-ylamino)methyl]-1H-pyrrole-2,4-dicarboxylate
53	2-tert-butyl 4-ethyl 3-ethyl-5-{{[(3-methoxypropyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate
54	2-tert-butyl 4-ethyl 3-ethyl-5-[(ethylamino)methyl]-1H-pyrrole-2,4-dicarboxylate
55	2-tert-butyl 4-ethyl 5-[(butylamino)methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate
56	2-tert-butyl 4-ethyl 3-ethyl-5-{{[(3-methoxyphenyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate

57	4-([5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl)amino)butanoic acid
58	2-tert-butyl 4-ethyl 3-ethyl-5-[(methylamino)methyl]-1H-pyrrole-2,4-dicarboxylate
59	2-tert-butyl 4-ethyl 3-ethyl-5-[(isobutylamino)methyl]-1H-pyrrole-2,4-dicarboxylate
60	2-tert-butyl 4-ethyl 3-ethyl-5-[(pentylamino)methyl]-1H-pyrrole-2,4-dicarboxylate
61	2-tert-butyl 4-ethyl 5-([2-(aminosulfonyl)ethyl]amino)methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate
62	2-tert-butyl 4-ethyl 3-ethyl-5-([(1H-pyrrol-2-ylmethyl)amino]methyl)-1H-pyrrole-2,4-dicarboxylate
63	2-tert-butyl 4-ethyl 5-([(4-chlorophenyl)amino]methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate
64	2-tert-butyl 4-ethyl 5-([(3-chlorophenyl)amino]methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate
65	2-tert-butyl 4-ethyl 5-([(2-chlorophenyl)amino]methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate
66	2-tert-butyl 4-ethyl 5-([(3-bromophenyl)amino]methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate
67	2-tert-butyl 4-ethyl 5-([(2-bromophenyl)amino]methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate
68	2-tert-butyl 4-ethyl 3-ethyl-5-([(4-fluorophenyl)amino]methyl)-1H-pyrrole-2,4-dicarboxylate
69	2-tert-butyl 4-ethyl 3-ethyl-5-([(3-fluorophenyl)amino]methyl)-1H-pyrrole-2,4-dicarboxylate
70	2-tert-butyl 4-ethyl 3-ethyl-5-([(2-fluorophenyl)amino]methyl)-1H-pyrrole-2,4-dicarboxylate
71	2-tert-butyl 4-ethyl 3-ethyl-5-[(pyridin-3-ylamino)methyl]-1H-pyrrole-2,4-dicarboxylate

72	2-tert-butyl 4-ethyl 5-{[(5-chloropyridin-2-yl)amino]methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate
73	2-tert-butyl 4-ethyl 5-{[(4-bromophenyl)amino]methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate
75	2-tert-butyl 4-methyl 3-ethyl-5-{[(4-pentylphenyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate
76	2-tert-butyl 4-methyl 5-[(1,1'-biphenyl-4-ylamino)methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate
77	2-tert-butyl 4-methyl 3-ethyl-5-{[(3,4,5-trimethoxyphenyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate
78	2-tert-butyl 4-methyl 3-ethyl-5-({[4-(5-methyl-4H-1,2,4-triazol-3-yl)phenyl]amino}methyl)-1H-pyrrole-2,4-dicarboxylate
79	2-tert-butyl 4-ethyl 3-ethyl-5-([[(2R)-5-oxopyrrolidin-2-yl]methyl]amino)methyl)-1H-pyrrole-2,4-dicarboxylate
81	diethyl 5-[(benzylamino)methyl]-3-methyl-1H-pyrrole-2,4-dicarboxylate
82	diethyl 3-methyl-5-{[(pyridin-2-ylmethyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate
83	diethyl 5-{[(2-chlorobenzyl)amino]methyl}-3-methyl-1H-pyrrole-2,4-dicarboxylate
84	diethyl 5-{[(3-chlorobenzyl)amino]methyl}-3-methyl-1H-pyrrole-2,4-dicarboxylate
85	diethyl 3-isopropyl-5-{[(pyridin-2-ylmethyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate
86	2-tert-butyl 4-ethyl 3-ethyl-5-{[(pyridin-2-ylmethyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate
87	4-benzyl 2-tert-butyl 3-ethyl-5-{[(4-methoxyphenyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate
88	5-(tert-butoxycarbonyl)-4-ethyl-2-{[(4-methoxyphenyl)amino]methyl}-1H-pyrrole-3-carboxylic acid
89	tert-butyl 3-ethyl-4-{[(2-hydroxyethyl)amino]carbonyl}-5-{[(4-

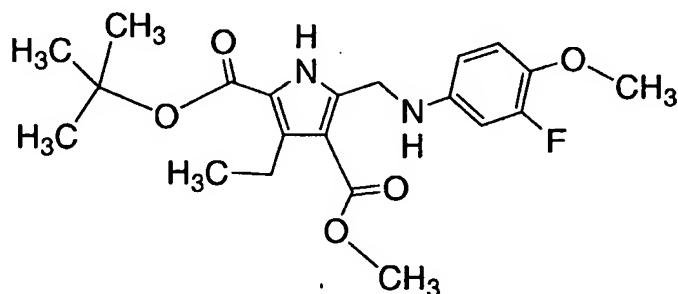
	methoxyphenyl)amino]methyl}-1H-pyrrole-2-carboxylate
90	tert-butyl 3-ethyl-4-[(ethylamino)carbonyl]-5-{[(4-methoxyphenyl)amino] methyl}-1H-pyrrole-2-carboxylate
91	tert-butyl 3-ethyl-5-{[(4-methoxyphenyl)amino]methyl}-4-{[(pyridin-2-ylmethyl)amino]carbonyl}-1H-pyrrole-2-carboxylate
92	tert-butyl 3-ethyl-5-{[(4-methoxyphenyl)amino]methyl}-4-{[(pyridin-4-ylmethyl)amino]carbonyl}-1H-pyrrole-2-carboxylate
93	tert-butyl 3-ethyl-5-{[(4-methoxyphenyl)amino]methyl}-4-[(propylamino) carbonyl]-1H-pyrrole-2-carboxylate
94	tert-butyl 3-ethyl-5-{[(4-methoxyphenyl)amino]methyl}-4-({[(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl]amino}carbonyl)-1H-pyrrole-2-carboxylate
95	tert-butyl 3-ethyl-5-{[(4-methoxyphenyl)amino]methyl}-4-{[(2-pyridin-2-ylethyl)amino]carbonyl}-1H-pyrrole-2-carboxylate
96	tert-butyl 3-ethyl-4-{[(1H-imidazol-2-ylmethyl)amino]carbonyl}-5-{[(4-methoxyphenyl)amino]methyl}-1H-pyrrole-2-carboxylate
97	tert-butyl 3-ethyl-5-{[(4-methoxyphenyl)amino]methyl}-4-({[(5-oxopyrrolidin-2-yl)methyl]amino}carbonyl)-1H-pyrrole-2-carboxylate
98	tert-butyl 3-ethyl-5-{[(4-methoxyphenyl)amino]methyl}-4-{[(pyridin-3-ylmethyl)amino]carbonyl}-1H-pyrrole-2-carboxylate
99	tert-butyl 4-{[(1H-benzimidazol-2-ylmethyl)amino]carbonyl}-3-ethyl-5-{[(4-methoxyphenyl)amino]methyl}-1H-pyrrole-2-carboxylate
100	tert-butyl 3-ethyl-4-{[(isoxazol-3-ylmethyl)amino]carbonyl}-5-{[(4-methoxyphenyl)amino]methyl}-1H-pyrrole-2-carboxylate
101	tert-butyl 4-({[2-(acetylamino)ethyl]amino}carbonyl)-3-ethyl-5-{[(4-methoxyphenyl)amino]methyl}-1H-pyrrole-2-carboxylate
102	tert-butyl 3-ethyl-5-{[(4-methoxyphenyl)amino]methyl}-4-({[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]amino}carbonyl)-1H-pyrrole-2-carboxylate
103	2-{{[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{[(4-methoxyphenyl)amino]methyl}-1H-pyrrol-3-yl)carbonyl]amino}ethanesulfonic acid

104	tert-butyl 4-[(benzylamino)carbonyl]-3-ethyl-5-{[(4-methoxyphenyl)amino]methyl}-1H-pyrrole-2-carboxylate
105	tert-butyl 3-ethyl-5-{[(4-methoxyphenyl)amino]methyl}-4-({[2-(5-methyl-4H-1,2,4-triazol-3-yl)ethyl]amino}carbonyl)-1H-pyrrole-2-carboxylate
106	tert-butyl 3-ethyl-5-{[(4-methoxyphenyl)amino]methyl}-4-({[2-(2-methyl-1,3-thiazol-4-yl)methyl]amino}carbonyl)-1H-pyrrole-2-carboxylate
107	tert-butyl 3-ethyl-5-{[(4-methoxyphenyl)amino]methyl}-4-({[2-(1H-pyrazol-4-yl)ethyl]amino}carbonyl)-1H-pyrrole-2-carboxylate
108	tert-butyl 3-ethyl-4-{[(1H-indol-6-ylmethyl)amino]carbonyl}-5-{[(4-methoxyphenyl)amino]methyl}-1H-pyrrole-2-carboxylate
109	tert-butyl 3-ethyl-5-{[(4-methoxyphenyl)amino]methyl}-4-({[2-methylimidazo[2,1-b][1,3]thiazol-6-yl)methyl]amino}carbonyl)-1H-pyrrole-2-carboxylate
110	tert-butyl 3-ethyl-5-{[(4-methoxyphenyl)amino]methyl}-4-({[5-methyl-4H-1,2,4-triazol-3-yl)methyl]amino}carbonyl)-1H-pyrrole-2-carboxylate
111	tert-butyl 3-ethyl-5-{[(4-methoxyphenyl)amino]methyl}-4-({[1-methyl-1H-pyrazol-4-yl)methyl]amino}carbonyl)-1H-pyrrole-2-carboxylate
112	tert-butyl 3-ethyl-5-{[(4-methoxyphenyl)amino]methyl}-4-({[1-methyl-5-oxopyrrolidin-2-yl)methyl]amino}carbonyl)-1H-pyrrole-2-carboxylate
113	tert-butyl 3-ethyl-4-({[2-(6-methoxy-1H-benzimidazol-2-yl)ethyl]amino}carbonyl)-5-{[(4-methoxyphenyl)amino]methyl}-1H-pyrrole-2-carboxylate
114	tert-butyl 3-ethyl-5-{[(4-methoxyphenyl)amino]methyl}-4-({[2-(1H-1,2,4-triazol-5-yl)ethyl]amino}carbonyl)-1H-pyrrole-2-carboxylate
115	tert-butyl 3-ethyl-5-{[(4-methoxyphenyl)amino]methyl}-4-({[1-methyl-1H-imidazol-2-yl)methyl]amino}carbonyl)-1H-pyrrole-2-carboxylate
116	tert-butyl 4-({[2,3-dihydroimidazo[2,1-b][1,3]thiazol-6-ylmethyl]amino}carbonyl)-3-ethyl-5-{[(4-methoxyphenyl)amino]methyl}-1H-pyrrole-2-carboxylate

117	tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-({[(4-methyl-1H-imidazol-2-yl)methyl]amino}carbonyl)-1H-pyrrole-2-carboxylate
118	tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-({[(8-methylimidazo[1,2-a]pyridin-2-yl)methyl]amino}carbonyl)-1H-pyrrole-2-carboxylate
119	tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-({[1-(5-methyl-4H-1,2,4-triazol-3-yl)ethyl]amino}carbonyl)-1H-pyrrole-2-carboxylate
120	tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-({[(quinolin-2-ylmethyl)amino]carbonyl)-1H-pyrrole-2-carboxylate
121	tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-({[(6-methylpyridin-2-yl)methyl]amino}carbonyl)-1H-pyrrole-2-carboxylate
122	tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-({[(4-methyl-1,3-thiazol-2-yl)methyl]amino}carbonyl)-1H-pyrrole-2-carboxylate
123	tert-butyl 4-{{[(6,7-dihydro-5H-cyclopenta[b]pyridin-3-ylmethyl)amino]carbonyl}-3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-1H-pyrrole-2-carboxylate
124	tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-({[(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-3-ylmethyl)amino]carbonyl)-1H-pyrrole-2-carboxylate
125	tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-({[2-(4-methyl-1,3-thiazol-5-yl)ethyl]amino}carbonyl)-1H-pyrrole-2-carboxylate
126	tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-({[(1-methylpiperidin-3-yl)methyl]amino}carbonyl)-1H-pyrrole-2-carboxylate
127	tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-({[(2-morpholin-4-yl-2-pyridin-4-ylethyl)amino]carbonyl)-1H-pyrrole-2-carboxylate
128	tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-({[(2-morpholin-4-yl-2-pyridin-3-ylethyl)amino]carbonyl)-1H-pyrrole-2-

	carboxylate
129	tert-butyl 3-ethyl-4-({[(5-fluoro-2-oxo-2,3-dihydro-1H-indol-3-yl)methyl] amino} carbonyl)-5-{{[(4-methoxyphenyl)amino]methyl}-1H-pyrrole-2-carboxylate
130	tert-butyl 4-({[(5-cyclopropyl-1H-pyrazol-3-yl)methyl]amino} carbonyl)-3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-1H-pyrrole-2-carboxylate
131	2-tert-butyl 4-ethyl 3-ethyl-5-{{hydroxy(pyridin-2-ylmethyl)amino} methyl}-1H-pyrrole-2,4-dicarboxylate
132	2-tert-butyl 4-(pyridin-2-ylmethyl) 3-ethyl-5-{{[(4-methoxyphenyl)amino] methyl}-1H-pyrrole-2,4-dicarboxylate
133	2-tert-butyl 4-ethyl 5-{{[(4-chlorophenyl)amino]methyl}-3-(2-phenylethyl)-1H-pyrrole-2,4-dicarboxylate
134	2-amino-N-{{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl} glycinamide
135	4-(Carbamoylmethyl-carbamoyl)-3-ethyl-5-[(4-methoxy-phenylamino)-methyl]-1H-pyrrole-2-carboxylic acid tert-butyl ester

EXAMPLE 137



5 2-tert-Butyl 4-methyl 3-ethyl-5-{{[(3-fluoro-4-methoxyphenyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate

2-tert-butyl 4-methyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate (28 mg, 0.1 mmol) and 3-fluoro-4-methoxyaniline (16 mg, 0.11 mmol.) were dissolved in HOAc-DCE (10/90, 1.5 mL). MP-cyanoborohydride (110 mg,

3.7mmol/g, 0.4 mmol) was added to the mixture solution. The reaction was shaken overnight at rt. After this period, the resin was filtered and washed with MeOH (1 mL). The collected solution was concentrated to afford the crude product. The crude material was then purified on an Agilent 1100 series Mass Guided HPLC purification system to afford the TFA salt of the product as a yellow solid.

5 Analytical LCMS: single peak (214 nm) at 3.537 min (CH₃CN/H₂O/1%TFA, 4 min gradient), M+1 peak *m/e* 407.2.

¹H NMR (300 MHz, free base in CDCl₃): δ 9.36 (s, 1H), 6.81 (t, *J*=9.0 Hz, 1H), 6.39 (dd, *J*=13.0, 2.8 Hz, 1H), 6.27-6.32 (m, 1H), 4.56 (s, 2H), 4.08(s, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 3.05 (q, *J*=7.3 Hz, 2H), 1.54 (s, 9H), 1.17 (t, *J*=7.3 Hz, 2H). HRMS: calc'd for C₂₁H₂₈FN₂O₅ (M+H), 407.1982; found

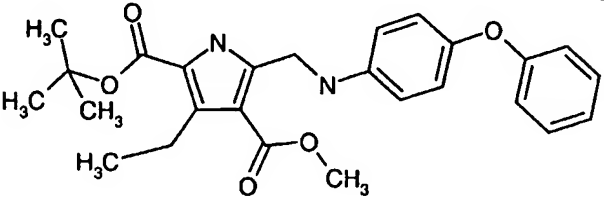
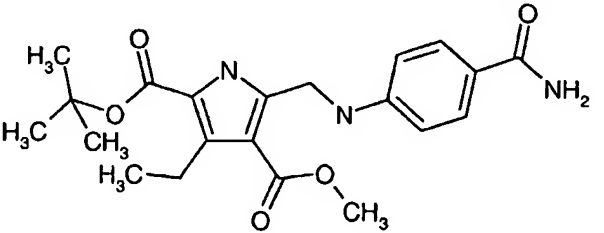
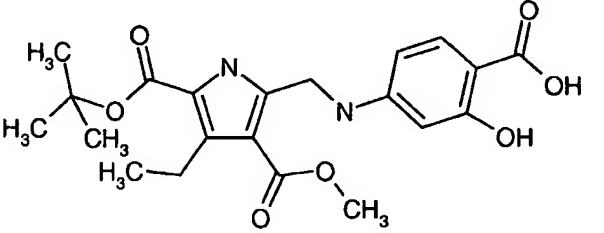
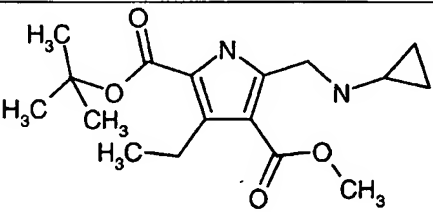
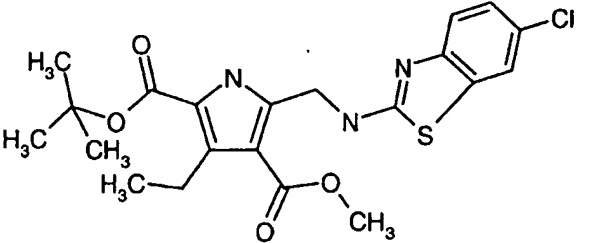
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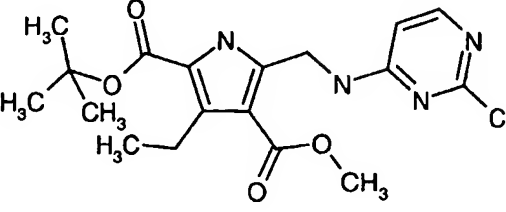
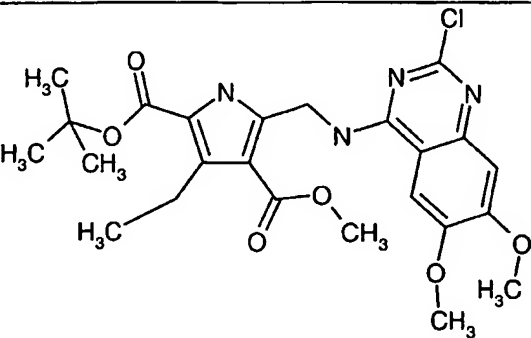
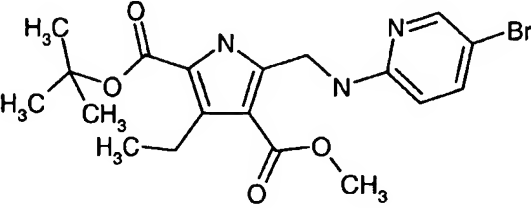
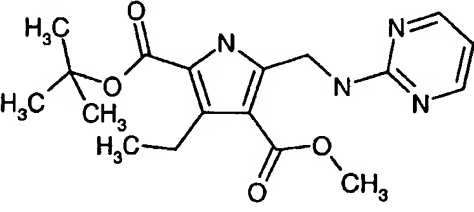
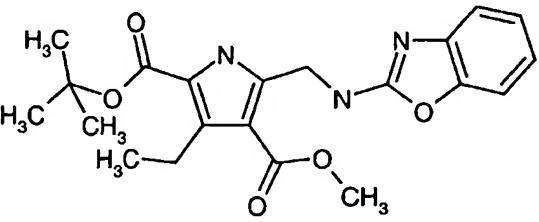
The compounds shown in the table below were also made as salts using the above-described techniques and are named in their free form.

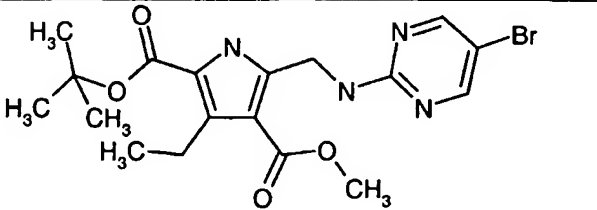
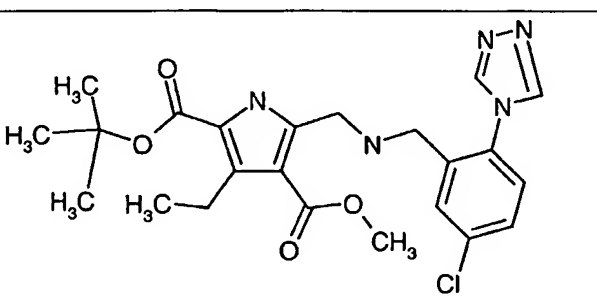
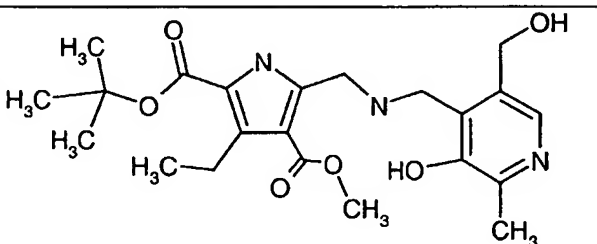
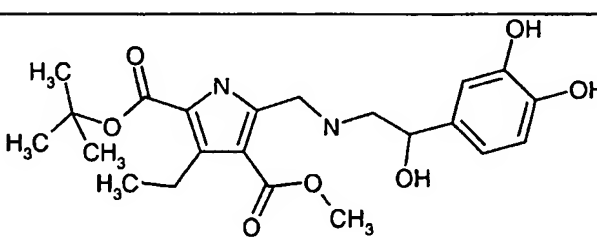
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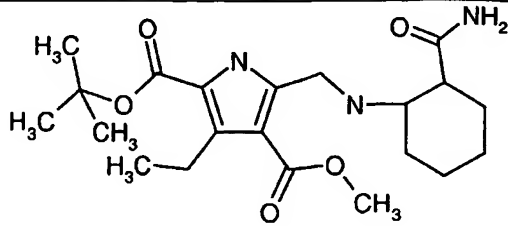
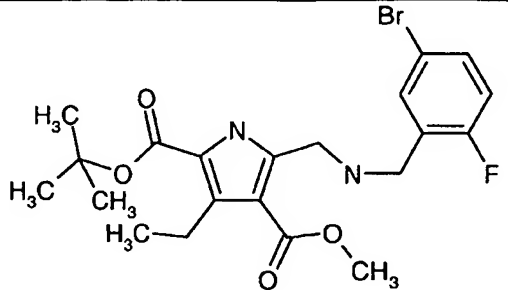
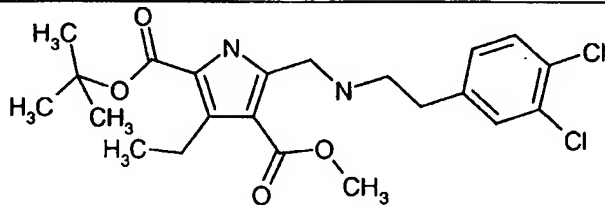
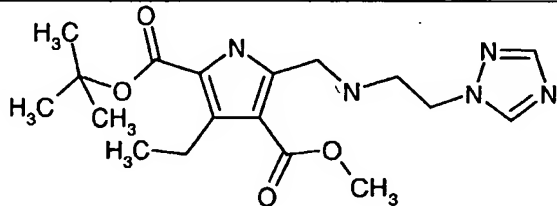
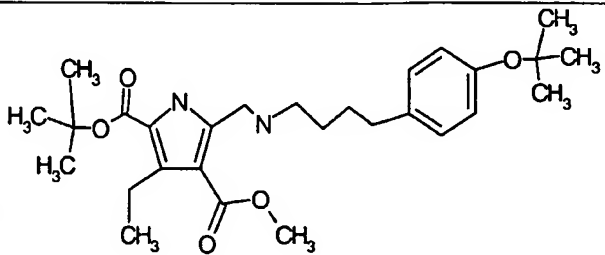
Chemical Name	Structure	MS
2-tert-butyl 4-methyl 3-ethyl-5-([(2-methyl-1,3-benzothiazol-6-yl)amino]methyl)-1H-pyrrole-2,4-dicarboxylate		430.2
2-tert-butyl 4-methyl 3-ethyl-5-([4-(1H-pyrazol-1-yl)phenyl]amino)methyl)-1H-pyrrole-2,4-dicarboxylate		425.2

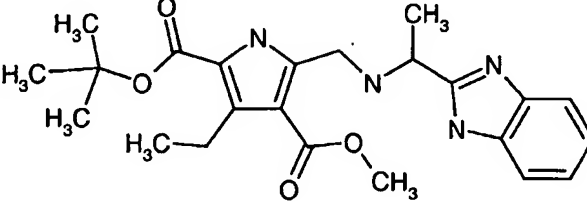
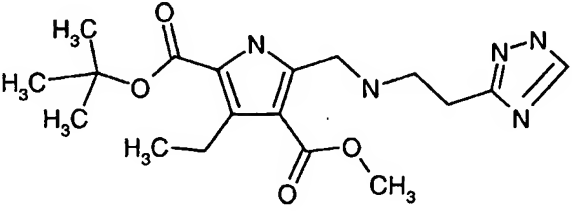
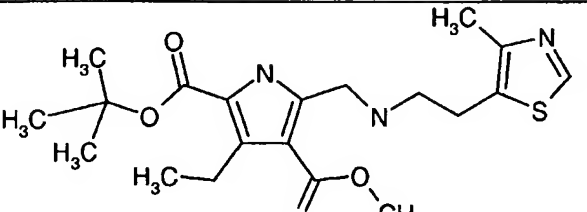
2-tert-butyl 4-methyl 3-ethyl-5-({[4-(2-oxoimidazolidin-1-yl)phenyl]amino} methyl)-1H-pyrrole-2,4-dicarboxylate		443.2
2-tert-butyl 4-methyl 3-ethyl-5-({[4-(3-methyl-2-oxoimidazolidin-1-yl)phenyl]amino} methyl)-1H-pyrrole-2,4-dicarboxylate		457.2
2-tert-butyl 4-methyl 3-ethyl-5-({[(3-fluoro-4-methoxyphenyl) amino]methyl}-1H-pyrrole-2,4-dicarboxylate		407.2
2-tert-butyl 4-methyl 5--{[(cyclopropylmethyl) amino]methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate		337.2

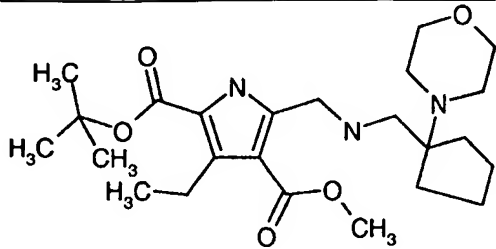
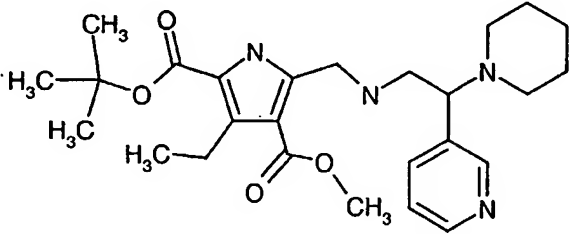
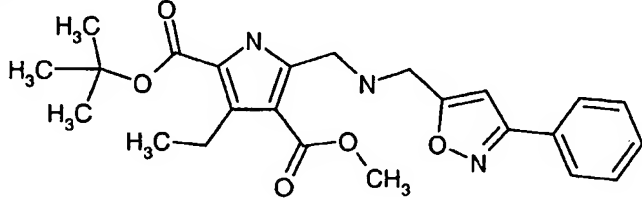
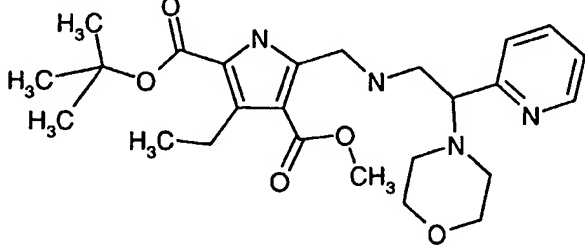
2-tert-butyl 4-methyl 3-ethyl-5-{[(4-phenoxyphenyl) amino] methyl}-1H-pyrrole-2,4-dicarboxylate		451.2
2-tert-butyl 4-methyl 5-([4-(aminocarbonyl) phenyl]amino) methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate		402.2
4-([5-(tert-butoxycarbonyl)-4-ethyl-3-(methoxycarbonyl)-1H-pyrrol-2-yl] methyl) amino)-2-hydroxybenzoic acid		419.2
2-tert-butyl 4-methyl 5-[(cyclopropylamino) methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate		323.2
2-tert-butyl 4-methyl 5-[[6-chloro-1,3-benzothiazol-2-yl] amino] methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate		450.2

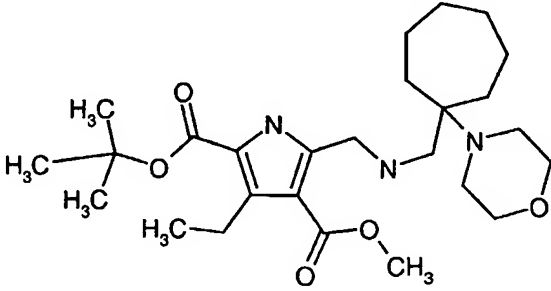
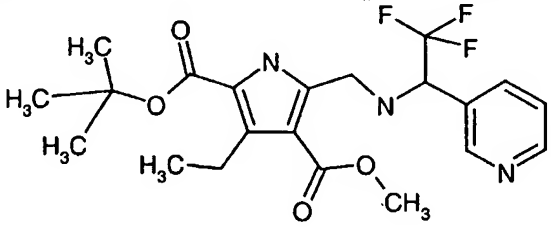
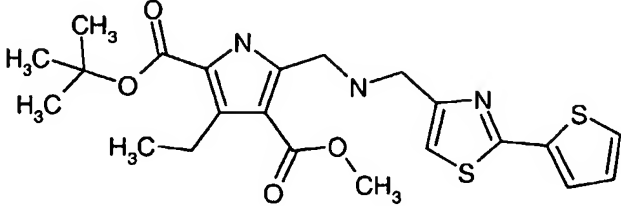
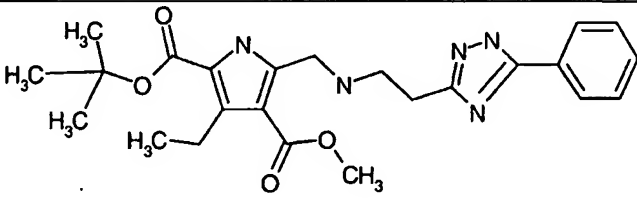
2-tert-butyl 4-methyl 5- {[(2-chloropyrimidin- 4-yl)amino]methyl}-3- ethyl-1H-pyrrole-2,4- dicarboxylate		395.1
2-tert-butyl 4-methyl 5- {[(2-chloro-6,7- dimethoxyquinazolin- 4-yl)amino]methyl}-3- ethyl-1H-pyrrole-2,4- dicarboxylate		505.2
2-tert-butyl 4-methyl 5- {[(5-bromopyridin-2- yl)amino]methyl}-3- ethyl-1H-pyrrole-2,4- dicarboxylate		439.1
2-tert-butyl 4-methyl 3- ethyl-5-[(pyrimidin-2- ylamino)methyl]-1H- pyrrole-2,4- dicarboxylate		361.2
2-tert-butyl 4-methyl 5- [(1,3-benzoxazol-2- ylamino)methyl]-3- ethyl-1H-pyrrole-2,4- dicarboxylate		400.2

2-tert-butyl 4-methyl 5- {[(5-bromopyrimidin- 2-yl)amino]methyl}-3- ethyl-1H-pyrrole-2,4- dicarboxylate		439.1
2-tert-butyl 4-methyl 5- (([5-chloro-2-(4H- 1,2,4-triazol-4- yl)benzyl] amino)methyl)-3-ethyl- 1H-pyrrole-2,4- dicarboxylate		474.2
2-tert-butyl 4-methyl 3- ethyl-5-([([3-hydroxy- 5-(hydroxymethyl)-2- methylpyridin-4- yl]methyl)amino) methyl]-1H-pyrrole- 2,4-dicarboxylate		434.2
2-tert-butyl 4-methyl 5- (([2-(3,4- dihydroxyphenyl)-2- hydroxyethyl]amino)m ethyl)-3-ethyl-1H- pyrrole-2,4- dicarboxylate		435.2

2-tert-butyl 4-methyl 5- ({[2-(aminocarbonyl) cyclohexyl]amino} methyl)-3-ethyl-1H- pyrrole-2,4- dicarboxylate		408.2
2-tert-butyl 4-methyl 5- {[(5-bromo-2- fluorobenzyl)amino]me thyl}-3-ethyl-1H- pyrrole-2,4- dicarboxylate		469.1
2-tert-butyl 4-methyl 5- ({[2-(3,4- dichlorophenyl) ethyl]amino}methyl)-3- ethyl-1H-pyrrole-2,4- dicarboxylate		455.1
2-tert-butyl 4-methyl 3- ethyl-5-({[2-(1H-1,2,4- triazol-1-yl)ethyl] amino}methyl)-1H- pyrrole-2,4- dicarboxylate		378.2
2-tert-butyl 4-methyl 5- ({[4-(4-tert- butoxyphenyl)butyl]am ino}methyl)-3-ethyl- 1H-pyrrole-2,4- dicarboxylate		487.3

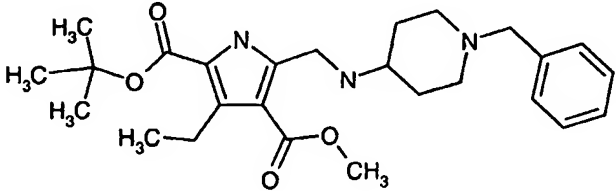
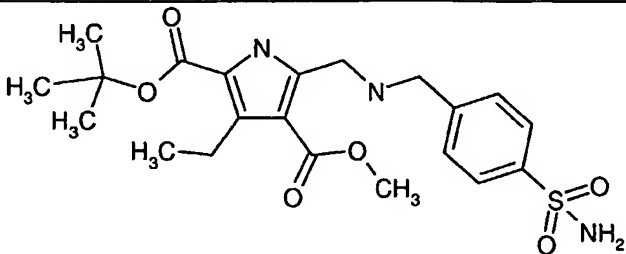
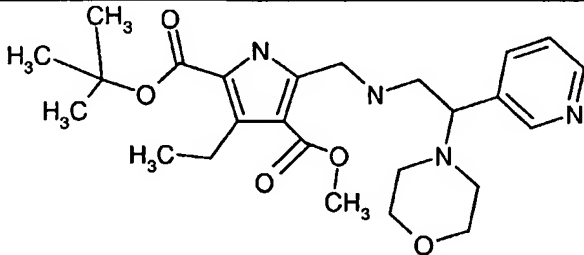
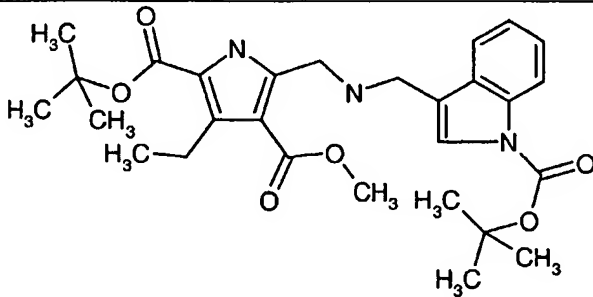
<p>2-tert-butyl 4-methyl 5- ({[1-(1H-benzimidazol- 2-yl) ethyl]amino} methyl)-3- ethyl-1H-pyrrole-2,4- dicarboxylate</p>		427.2
<p>2-tert-butyl 4-methyl 3- ethyl-5-({[2-(1H-1,2,4- triazol-3-yl) ethyl]amino} methyl) - 1H-pyrrole-2,4- dicarboxylate</p>		378.2
<p>2-tert-butyl 4-methyl 3- ethyl-5-({[2-(4-methyl- 1,3-thiazol-5- yl)ethyl]amino} methyl)-1H-pyrrole- 2,4-dicarboxylate</p>		408.2

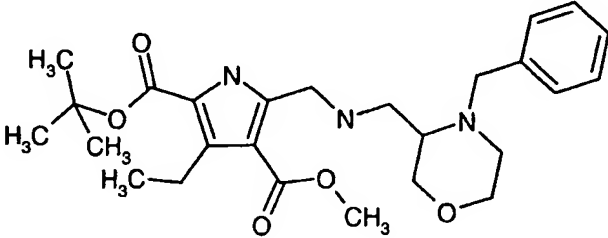
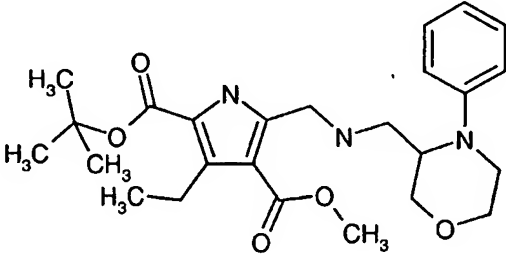
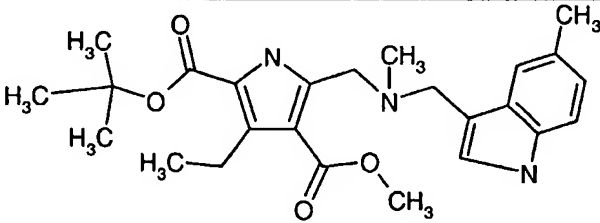
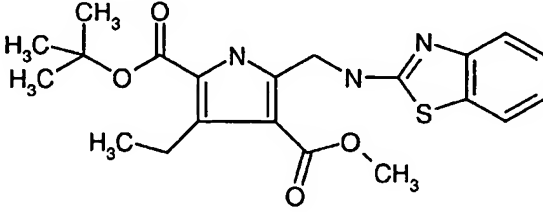
2-tert-butyl 4-methyl 3-ethyl-5-(((1-morpholin-4-ylcyclopentyl)methyl)amino)methyl)-1H-pyrrole-2,4-dicarboxylate		450.2
2-tert-butyl 4-methyl 3-ethyl-5-(((2-piperidin-1-yl-2-pyridin-3-ylethyl)amino)methyl)-1H-pyrrole-2,4-dicarboxylate		471.3
2-tert-butyl 4-methyl 3-ethyl-5-(((3-phenylisoxazol-5-yl)methyl)amino)methyl)-1H-pyrrole-2,4-dicarboxylate		440.2
2-tert-butyl 4-methyl 3-ethyl-5-(((2-morpholin-4-yl-2-pyridin-2-ylethyl)amino)methyl)-1H-pyrrole-2,4-dicarboxylate		473.3

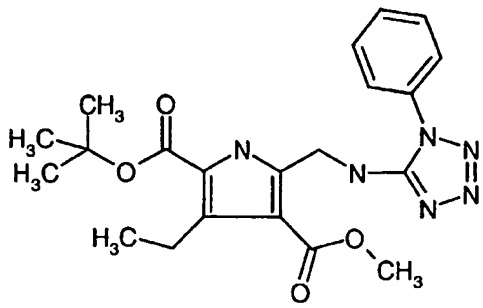
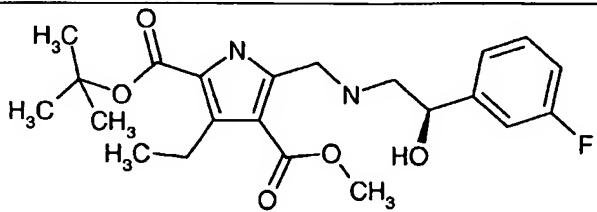
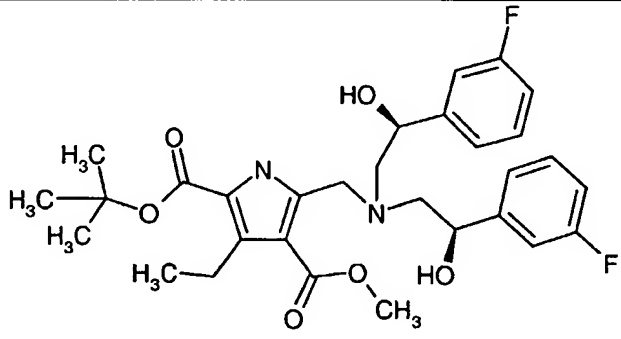
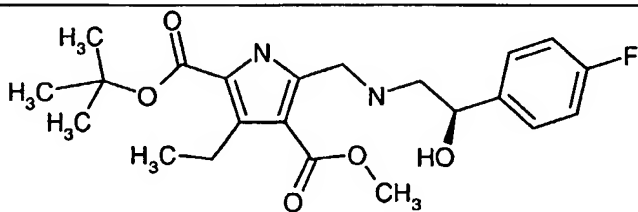
2-tert-butyl 4-methyl 3-ethyl-5-({[(1- morpholin-4- ylcycloheptyl)methyl] amino}methyl)- 1H-pyrrole-2,4- dicarboxylate		478.3
2-tert-butyl 4-methyl 3-ethyl-5-{{[(2,2,2- trifluoro-1-pyridin- 3-ylethyl)amino] methyl}}-1H-pyrrole- 2,4-dicarboxylate		442.2
2-tert-butyl 4-methyl 3-ethyl-5-({[(2- thien-2-yl-1,3- thiazol-4-yl)methyl] amino}methyl)-1H- pyrrole-2,4- dicarboxylate		462.1
2-tert-butyl 4-methyl 3-ethyl-5-({[2-(5- phenyl-1H-1,2,4- triazol-3-yl) ethyl] amino}methyl)-1H- pyrrole-2,4- dicarboxylate		454.2

2-tert-butyl 4-methyl 3-ethyl-5-({[(6-methoxy-1H-benzimidazol-2-yl)methyl]amino)methyl}-1H-pyrrole-2,4-dicarboxylate		443.2
2-tert-butyl 4-methyl 5-{{[(2,3-dihydro-1,4-benzodioxin-2-yl)methyl]amino)methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate		431.2
2-tert-butyl 4-methyl 3-ethyl-5-({methyl[(5-phenylisoxazol-3-yl)methyl]amino)methyl}-1H-pyrrole-2,4-dicarboxylate		454.2
2-tert-butyl 4-methyl 3-ethyl-5-[(quinoxalin-2-ylamino)methyl]-1H-pyrrole-2,4-dicarboxylate		411.2

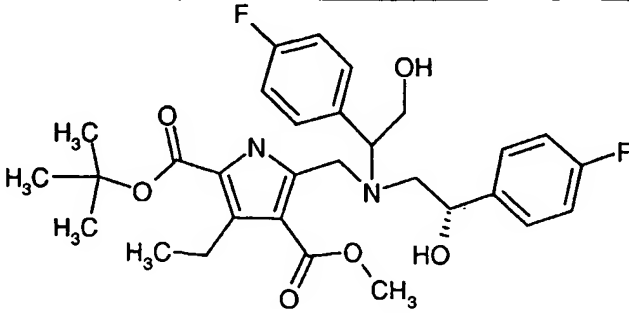
2-tert-butyl 4-methyl 5-[[[(1,2- diphenylethyl) amino]methyl]-3- ethyl-1H-pyrrole- 2,4-dicarboxylate		463.3
2-tert-butyl 4-methyl 5-[[[(2,2- diphenylethyl) amino]methyl]-3- ethyl-1H-pyrrole- 2,4-dicarboxylate		463.3
2-tert-butyl 4-methyl 5-[[[(2-[4- (aminosulfonyl) phenyl]ethyl)amino] methyl]-3-ethyl-1H- pyrrole-2,4- dicarboxylate		466.2
2-tert-butyl 4-methyl 5-[[[(3,4- dihydroxybenzyl) amino]methyl]-3- ethyl-1H-pyrrole- 2,4-dicarboxylate		405.2

2-tert-butyl 4-methyl 5-(((1-benzylpiperidin-4-yl)amino)methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate		456.3
2-tert-butyl 4-methyl 5-(((4-(aminosulfonyl)benzyl)amino)methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate		452.2
2-tert-butyl 4-methyl 3-ethyl-5-(((2-morpholin-4-yl-2-pyridin-3-ylethyl)amino)methyl)-1H-pyrrole-2,4-dicarboxylate		473.3
2-tert-butyl 4-methyl 5-((((1-(tert-butoxycarbonyl)-1H-indol-3-yl)methyl)amino)methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate		512.3

2-tert-butyl 4-methyl 5-(((4-benzylmorpholin-3-yl)methyl)amino) methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate		472.3
2-tert-butyl 4-methyl 3-ethyl-5-(((4-phenylmorpholin-3-yl)methyl)amino) methyl)-1H-pyrrole-2,4-dicarboxylate		458.3
2-tert-butyl 4-methyl 3-ethyl-5-((methyl[(5-methyl-1H-indol-3-yl)methyl]amino) methyl)-1H-pyrrole-2,4-dicarboxylate		440.2
2-tert-butyl 4-methyl 5-[(1,3-benzothiazol-2-ylamino)methyl]- 3-ethyl-1H-pyrrole-2,4-dicarboxylate		416.2

2-tert-butyl 4-methyl 3-ethyl-5-([(1-phenyl-1H-tetrazol-5-yl)amino] methyl)-1H-pyrrole-2,4-dicarboxylate		427.2
2-tert-butyl 4-methyl 3-ethyl-5-([(2R)-2-(3-fluorophenyl)-2-hydroxyethyl]amino] methyl)-1H-pyrrole-2,4-dicarboxylate		421.2
2-tert-butyl 4-methyl 3-ethyl-5-([(2R)-2-(3-fluorophenyl)-2-hydroxyethyl][(2S)-2-(3-fluorophenyl)-2-hydroxyethyl] amino] methyl)-1H-pyrrole-2,4-dicarboxylate		559.3
2-tert-butyl 4-methyl 3-ethyl-5-([(2R)-2-(4-fluorophenyl)-2-hydroxyethyl]amino] methyl)-1H-pyrrole-2,4-dicarboxylate		421.2

2-tert-butyl 4-methyl 5-({bis[(2R)-2-(4- fluorophenyl)-2- hydroxyethyl]amino }methyl)-3-ethyl- 1H-pyrrole-2,4- dicarboxylate		559.3
2-tert-butyl 4-methyl 3-ethyl-5-({[(2S)-2- (4-fluorophenyl)-2- hydroxyethyl]amino }methyl)-1H-pyrrole -2,4-dicarboxylate		421.2
2-tert-butyl 4-methyl 3-ethyl-5-({[1-(4- fluorophenyl)-2- hydroxyethyl]amino }methyl)-1H-pyrrole -2,4-dicarboxylate		421.2
2-tert-butyl 4-methyl 5-({bis[(2S)-2-(4- fluorophenyl)-2- hydroxyethyl]amino }methyl)-3-ethyl- 1H-pyrrole-2,4- dicarboxylate		559.3

2-tert-butyl 4-methyl 3-ethyl-5-([(2S)-2- (4-fluorophenyl)-2- hydroxyethyl][1-(4- fluorophenyl)-2- hydroxyethyl]amino }methyl)-1H-pyrrole -2,4-dicarboxylate		559.3
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ASSAYS

5 The compounds of the instant invention described in the Examples above were tested by the assays described below and were found to have kinase inhibitory activity. In particular, the compounds of the instant invention inhibited IGF-1R or insulin receptor kinase activity with an IC₅₀ of less than or equal to about 100 μM. Other assays are known in the literature and could be readily performed by

10 those with skill in the art (see for example, Dhanabal *et al.*, *Cancer Res.* 59:189-197; Xin *et al.*, *J. Biol. Chem.* 274:9116-9121; Sheu *et al.*, *Anticancer Res.* 18:4435-4441; Ausprunk *et al.*, *Dev. Biol.* 38:237-248; Gimbrone *et al.*, *J. Natl. Cancer Inst.* 52:413-427; Nicosia *et al.*, *In Vitro* 18:538-549).

15 IGF-1R KINASE ASSAY

IGF-1R receptor kinase activity is measured by incorporation of phosphate into a peptide substrate containing a tyrosine residue. Phosphorylation of the peptide substrate is quantitated using anti-IGF-1R and anti-phosphotyrosine antibodies in an HTRF (Homogeneous Time Resolved Fluorescence) detection

20 system. (Park, Y-W., et al. *Anal. Biochem.*, (1999) 269, 94-104)

Materials

IGF-1R Receptor Kinase Domain

The intracellular kinase domain of human IGF-1R was cloned as a
5 glutathione S-transferase fusion protein. IGF-1R β -subunit amino acid residues 930
to 1337 (numbering system as per Ullrich et al., EMBO J. (1986) 5, 2503-2512) were
cloned into the baculovirus transfer vector pAcGHLT-A (BD-Pharmingen) such that
the N-terminus of the IGF-1R residues are fused to the C-terminus of the GST domain
encoded in the transfer vector pAcGHLT-A. Recombinant virus was generated and
10 the fusion protein expressed in SF-9 insect cells (BD-Pharmingen). Enzyme was
purified by means of a glutathione sepharose column.

Insulin Receptor Kinase Domain

The intracellular kinase domain of human insulin receptor was cloned
15 as a glutathione S-transferase fusion protein. Insulin receptor β -subunit amino acid
residues 941 to 1343 (numbering system as per Ullrich et al., Nature, (1985) 313, 756-
761) were cloned into the baculovirus transfer vector pAcGHLT-A (BD-Pharmingen)
such that the N-terminus of the IGF-1R residues are fused to the C-terminus of the
GST domain encoded in the transfer vector pAcGHLT-A. Recombinant virus was
20 generated and the fusion protein expressed in SF-9 insect cells (BD-Pharmingen)
Enzyme was purified by means of a glutathione sepharose column.

Insect Cell Lysis Buffer

10mM Tris pH 7.5; 130mM NaCl; 2mM DTT; 1% Triton X-100; 10mM NaF;
25 10mM NaPi; 10mM NaPPi; 1X protease inhibitor cocktail (Pharmingen).

Wash Buffer

Phosphate Buffered Saline (PBS): 137mM NaCl, 2.6mM KCl, 10mM Na₂HPO₄,
1.8mM KH₂PO₄, pH 7.4; 1mM DTT; 1X protease inhibitor cocktail

Dialysis Buffer

20mM Tris pH 7.5; 1mM DTT; 200mM NaCl; 0.05% Triton X-100 and 50% glycerol

Enzyme Dilution Buffer

- 5 50mM Tris pH 7.5; 1mM DTT; 100mM NaCl; 10% glycerol; 1mg/ml BSA

Enzyme Reaction Buffer

20mM Tris pH 7.4; 100mM NaCl; 1mg/ml BSA; 5mM MgCl₂; 2mM DTT

- 10 Quench Buffer

125mM Tris pH 7.8; 75mM EDTA; 500mM KF; 0.125% Triton X-100; 1.25% BSA; 60 nM SA-XL665 (Packard); 300 pM europium cryptate labeled anti-phosphotyrosine antibody (Eu-PY20)

- 15 Peptide Substrate

Sequence LCB-EQEDEPEGDYFEWLE-NH₂; stock solution is 1mM dissolved in DMSO; diluted to 1uM in 1X enzyme reaction buffer for 10X working stock. (LCB = aminohexanoylbiotin)

- 20 ATP

Stock solution is 0.5 M ATP (Boehringer) pH 7.4; stock solution is diluted to 40mM ATP in enzyme reaction buffer to give 20X working stock solution

HEK-21 Cell Line

- 25 Human embryonic kidney cells (HEK-293) (ATCC) were transfected with an expression plasmid containing the entire IGF-1R coding sequence. After antibiotic selection, colonies were screened for IGF-1R overexpression by western blot analysis. One clone, designated HEK-21 was selected for cell based IGF-1R autophosphorylation assays.

30

HEK Cell Growth Media

Dulbecco's Modified Eagle's Media (DMEM), 10% Fetal Calf Serum, 1X Penn/Strep, 1X Glutamine, 1X Non-essential amino acids (all from Life Technologies)

5 Cell Lysis Buffer

50mM Tris-HCl pH 7.4; 150mM NaCl; 1% Triton X-100 (Sigma); 1X Mammalian protease inhibitors (Sigma); 10mM NaF; 1mM NaVanadate

Western Blocking Buffer

10 20mM Tris-HCl pH 8.0; 150mM NaCl; 5% BSA (Sigma); 0.1% Tween 20 (Biorad)

MethodsA. Protein Purifications

15 *Spodoptera frugiperda* SF9 cells were transfected with recombinant virus encoding either the GST-IGF-1R β -subunit or GST-InsR fusion protein at an MOI of 4 virus particles/cell. Cells are grown for 48 hours at 27°C, harvested by centrifugation and washed once with PBS. The cell pellet is frozen at -70°C after the final centrifugation. All subsequent purification steps are performed at 4°C. 10 grams
20 of frozen cell paste is thawed in a 90ml volume of insect cell lysis buffer (BD-Pharmingen) and held on ice with occasional agitation for 20 minutes. The lysate is centrifuged at 12000g to remove cellular debris. Lysis supernatant was mixed with 45ml of glutathione agarose beads (BD-Pharmingen) and agitated slowly at 4°C for one hour after which the beads were centrifuged and washed 3X with wash buffer.
25 The beads are resuspended in 45 ml of wash buffer and poured as a slurry into a chromatography column. The column is washed with 5 volumes of wash buffer and the GST-IGF-1R is eluted from the column with 5mM Glutathione in wash buffer. Pooled fractions are dialyzed vs. dialysis buffer and stored at -20°C.

B. IGF-1R Kinase Assay

The IGF-1R enzyme reaction is run in a 96 well plate format. The enzyme reaction consists of enzyme reaction buffer plus 0.1nM GST-IGF-1R, 100 nM peptide substrate and 2mM ATP in a final volume of 60 microliters. Inhibitor, in
5 DMSO, is added in a volume 1 microliter and preincubated for 10 minutes at 22°C. Final inhibitor concentration can range from 100uM to 1nM. The kinase reaction is initiated with 3 microliters of 40mM ATP. After 20 minutes at 22°C, the reaction is stopped with 40 microliters of quench buffer and allowed to equilibrate for 2 hours at 22°C. Relative fluorescent units are read on a Discovery plate reader (Packard).
10 IC50s for compounds are determined by 4 point sigmoidal curve fit.

C. Insulin Receptor Kinase Assay

The kinase reaction for insulin receptor is identical to that used to assay IGF-1R (above), except that GST-InsR is substituted at a final concentration of
15 0.1nM.

D. Cell Based IGF-1R Autophosphorylation Assay

IGF-1R inhibitor compounds are tested for their ability to block IGF-I induced IGF-1R autophosphorylation in a IGF-1R transfected human embryonic
20 kidney cell line (HEK-21). HEK-21 cells over-expressing the human IGF-1R receptor are cultured in 6-well plates (37°C in a 5% CO₂ atmosphere) in HEK cell growth media to 80% of confluence. Cells are serum starved for four hours in HEK growth media with 0.5% fetal calf serum. A 10X concentration of inhibitor in growth media is added to the cells in one-tenth the final media volume and allowed to
25 preincubate for one hour at 37°C. Inhibitor concentration can range from 10nM to 100uM. IGF-I (Sigma) is added to the serum starved cells to a final concentration of 30ng/ml. After a 10 minute incubation in the presence of IGF-I at 37°C, the media is removed, the cells washed once with PBS and 0.5mls of cold cell lysis buffer added. After 5 minutes incubation on ice, cells are scraped from the wells and lysis buffer
30 plus cells are transferred to a 1.5ml microfuge tube. The total lysate is held at 4°C for

twenty minutes and then centrifuged at top speed in a microfuge. The supernatant is removed and saved for analysis. Phosphorylation status of the receptor is assessed by Western blot. Lysates are electrophoresed on 8% denaturing Tris-Glycine polyacrylamide gels and the proteins transferred to nitrocellulose filters by electro-

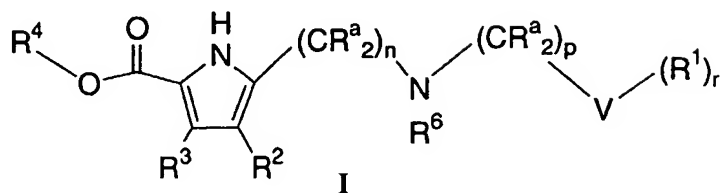
5 blotting. The blots are blocked with blocking reagent for 10 minutes after which anti-phosphotyrosine antibody (4G10, Upstate Biotechnology) is added to a final dilution of 1:1500. Blots and primary antibody are incubated at 4°C overnight. After washing with PBS plus 0.2% Tween 20 (Biorad), an HRP conjugated anti-mouse secondary antibody (Jackson Labs) is added at a dilution of 1:15000 and incubated at

10 4°C for 2 hours. Blots are then washed with PBS-Tween and developed using ECL (Amersham) luminescent reagent. Phosphorylated IGF-1R on the blots is visualized by autoradiography or imaging using a Kodak Image Station 440. IC50s are determined through densitometric scanning or quantitation using the Kodak Digital Science software.

15

WHAT IS CLAIMED IS:

1. A compound of Formula I



wherein

5

V is selected from

- 1) C₁-C₁₀ alkyl,
- 2) aryl,
- 3) heterocycle,
- 10 4) C₃-C₁₀ cycloalkyl, and
- 5) -C(O);

R^a is independently selected from

- 1) H,
- 15 2) OR⁷,
- 3) unsubstituted or substituted C₁-C₁₀ alkyl
- 4) unsubstituted or substituted aryl, and
- 5) unsubstituted or substituted heterocycle;

20 R^b is independently selected from

- 1) H,
- 2) OR⁷,
- 3) unsubstituted or substituted C₁-C₁₀ alkyl,
- 4) unsubstituted or substituted aryl, and
- 25 5) unsubstituted or substituted heterocycle;

R¹ is independently selected from

- 1) H,
- 2) unsubstituted or substituted C₁-C₁₀ alkyl,
- 3) unsubstituted or substituted C₃-C₁₀ cycloalkyl,
- 5 4) unsubstituted or substituted aryl,
- 5) unsubstituted or substituted heterocycle,
- 6) OR⁷,
- 7) C(O)R⁷,
- 8) C(O)OR⁷,
- 10 9) C(O)N(R⁷)₂,
- 10) N(R⁷)₂,
- 11) halo, and
- 12) -S(O)₂N(R⁵)₂;

15 R² is selected from

- 1) unsubstituted or substituted C₁-C₁₀ alkyl,
- 2) -C(O)OR⁷,
- 3) unsubstituted or substituted aryl,
- 4) -(CR^b₂)_nN(R⁷)₂,
- 20 5) -C(O)N(R⁷)₂,
- 6) -C(O)NHR⁷OR⁷,
- 7) -C(O)NH(CR^b₂)_qR⁷,
- 8) -C(O)NHR⁷NHC(O)R⁷,
- 9) -C(O)NHR⁷S(O)₂OR⁷,
- 25 10) (CR^b₂)_nOR⁷, and
- 11) -C(O)NH(CR^b₂)_qC(O)N(R⁷)₂;

R³ is selected from

- 1) H,
- 2) unsubstituted or substituted C₁-C₁₀ alkyl,
- 3) unsubstituted or substituted aralkyl
- 5 4) unsubstituted or substituted aryl,
- 5) unsubstituted or substituted heterocycle, and
- 6) unsubstituted or substituted heterocyclalkyl;

R⁴ is selected from

- 10 1) unsubstituted or substituted C₁-C₁₀ alkyl,
- 2) unsubstituted or substituted aryl,
- 3) unsubstituted or substituted aralkyl, and
- 4) unsubstituted or substituted heterocycle;

15 R⁵ is independently selected from

- 1) H,
- 2) unsubstituted or substituted C₁-C₁₀ alkyl,
- 3) unsubstituted or substituted aryl, and
- 4) unsubstituted or substituted heterocycle;

20

R⁶ is independently selected from

- 1) H,
- 2) unsubstituted or substituted C₁-C₁₀ alkyl,
- 3) unsubstituted or substituted aryl,
- 25 4) unsubstituted or substituted heterocycle,
- 5) OR⁷,
- 6) unsubstituted or substituted aralkyl, and
- 7) unsubstituted or substituted heterocyclalkyl;

R⁷ is independently selected from

- 1) H,
- 2) unsubstituted or substituted C₁-C₁₀ alkyl,
- 3) unsubstituted or substituted aralkyl,
- 5 4) unsubstituted or substituted aryl,
- 5) unsubstituted or substituted heterocycle, and
- 6) unsubstituted or substituted heterocyclalkyl;

n is 0 to 6,

10 p is 0 to 6,

q is 0 to 5, and

r is 0 to 6;

or a pharmaceutically acceptable salt or stereoisomer thereof.

15

2. The compound of Claim 1 wherein:

R⁴ is selected from

- 1) unsubstituted or substituted C₁-C₁₀ alkyl, and
- 20 2) unsubstituted or substituted aryl;

or a pharmaceutically acceptable salt or stereoisomer thereof.

3. The compound of Claim 2 wherein:

25

R¹ is independently selected from

- 1) H,
- 2) unsubstituted or substituted C₁-C₁₀ alkyl,
- 3) unsubstituted or substituted C₃-C₁₀ cycloalkyl,
- 30 4) OR⁷,

- 5) $C(O)R^7$,
 6) $C(O)OR^7$,
 7) $C(O)N(R^7)_2$,
 8) $N(R^7)_2$,
 5 9) halo, and
 10) $-S(O)_2N(R^5)_2$;

- n is 0 to 2,
 p is 0 to 4,
 10 q is 0 to 3, and
 r is 0 to 4,

or a pharmaceutically acceptable salt or stereoisomer thereof.

- 15 4. The compound of Claim 1 selected from:

2-tert-butyl 4-ethyl 3-benzyl-5-[[(4-chlorophenyl)amino]methyl]-1H-pyrrole-2,4-dicarboxylate;

- 20 [5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-[(5-oxopyrrolidin-2-yl)methyl]methanaminium trifluoroacetate;

[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-(1H-indol-2-ylmethyl)methanaminium trifluoroacetate;

- 25 N-[[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl]-3,4-dichlorobenzenaminium trifluoroacetate;

- 30 N-[[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl]-4-methylbenzenaminium trifluoroacetate;

N-{{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-4-hydroxybenzenaminium trifluoroacetate;

5 N-{{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-4-methoxybenzenaminium trifluoroacetate;

N-{{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-4-chloro-N-methylbenzenaminium trifluoroacetate;

10 2-[[[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl]ammonio)methyl]-6-methylpyridinium bis(trifluoroacetate);

3-[[[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl]ammonio)methyl]-5-cyclopropyl-1H-pyrazol-1-ium bis(trifluoroacetate);

15 [5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-[(3,5-dimethyl-1H-pyrazol-4-yl)methyl]methanaminium trifluoroacetate;

20 [5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-[(5-phenyl-1,3,4-oxadiazol-2-yl)methyl]methanaminium trifluoroacetate;

2-[[[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl]ammonio)methyl]-1H-imidazol-1-ium bis(trifluoroacetate);

25 5-[[[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl]ammonio)methyl]-3-methyl-4H-1,2,4-triazole-1,4-diiium tris(trifluoroacetate);

6-[[[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl]ammonio)methyl]-2-methylimidazo[2,1-b][1,3]thiazol-7-ium bis(trifluoroacetate);

30

- 2-([5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl) ammonio)methyl]-4-methyl-1H-imidazol-3-ium bis(trifluoroacetate);
- 2-([5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl) ammonio)methyl]-1-methyl-1H-imidazol-3-ium bis(trifluoroacetate);
- 5 [5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-[(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl]methanaminium trifluoroacetate;
- 10 5-([5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl) ammonio)methyl]-1H-1,2,4-triazol-1-ium bis(trifluoroacetate);
- 6-([5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl) ammonio)methyl]imidazo[2,1-b][1,3]thiazol-4-ium bis(trifluoroacetate);
- 15 2-([5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl) ammonio)methyl]-5-chloro-3H-benzimidazol-1-ium bis(trifluoroacetate);
- [5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-[(4-oxo-3,4-dihydrophthalazin-1-yl)methyl]methanaminium trifluoroacetate;
- 20 [5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-(1H-indol-6-yl)methyl]methanaminium trifluoroacetate;
- 25 [5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-[(4-methyl-1,3-thiazol-2-yl)methyl]methanaminium trifluoroacetate;
- 2-([5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl) ammonio)methyl]-8-methylimidazo[1,2-a]pyridin-4-ium bis(trifluoroacetate);
- 30

- 2-([5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl) ammonio)methyl]-3H-benzimidazol-1-ium bis(trifluoroacetate);
- 5 N-{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-3-methylbenzenaminium trifluoroacetate;
- N-{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-4-isopropylbenzenaminium trifluoroacetate;
- 10 N-{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-4-ethylbenzenaminium trifluoroacetate;
- N-{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-3,5-dimethylbenzenaminium trifluoroacetate;
- 15 N-{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-3,4-dimethoxybenzenaminium trifluoroacetate;
- 2-2-([5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl) ammonio)ethyl]pyridinium bis(trifluoroacetate);
- 20 [5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-[(1-methyl-1H-pyrazol-4-yl)methyl]methanaminium trifluoroacetate;
- 25 N-{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-4-ethoxybenzenaminium trifluoroacetate;
- N-{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-3,4-dimethylbenzenaminium trifluoroacetate;
- 30

- N-{{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}}-1,3-benzodioxol-5-aminium trifluoroacetate;
- 5 N-{{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}}-4-isopropoxybenzenaminium trifluoroacetate;
- 4-(((5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl)methyl}ammonio)methyl)-1,3-thiazol-3-ium bis(trifluoroacetate);
- 10 5-(((5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl)methyl}ammonio)methyl)-1,3-thiazol-3-ium bis(trifluoroacetate);
- 2-(((5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl)methyl}ammonio)methyl)-1,3-thiazol-3-ium bis(trifluoroacetate);
- 15 [5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-(isoxazol-5-ylmethyl)methanaminium trifluoroacetate;
- [5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-[(1,5-dimethyl-1H-pyrazol-4-yl)methyl]methanaminium trifluoroacetate;
- 20 [5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-4-tert-butylbenzenaminium trifluoroacetate;
- 25 2-tert-butyl 4-ethyl 5-({[4-(dimethylamino)phenyl]amino}methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate bis(trifluoroacetate);
- N-{{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}}-2-methylbenzenaminium trifluoroacetate;
- 30

- N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl}methyl}-2-methoxybenzenaminium trifluoroacetate;
- 5 N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl}methyl}-4-propylbenzenaminium trifluoroacetate;
- N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl}methyl}-2,5-dimethoxybenzenaminium trifluoroacetate;
- 10 N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl}methyl}-4-butylbenzenaminium trifluoroacetate;
- N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl}methyl}-3-hydroxy-4-methoxybenzenaminium trifluoroacetate;
- 15 N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl}methyl}-1H-indol-4-aminium trifluoroacetate;
- N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl}methyl}-1H-indol-6-aminium trifluoroacetate;
- 20 N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl}methyl}-3-methoxypropan-1-aminium trifluoroacetate;
- 25 N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl}methyl}ethanaminium trifluoroacetate;
- N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl}methyl}butan-1-aminium trifluoroacetate;
- 30

N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl}methyl}-3-methoxybenzenaminium trifluoroacetate;

5 N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl}methyl}-3-carboxypropan-1-aminium trifluoroacetate;

[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-methylmethanaminium trifluoroacetate;

10 N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl}methyl}-2-methylpropan-1-aminium trifluoroacetate;

N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl}methyl}pentan-1-aminium trifluoroacetate;

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2-(aminosulfonyl)-N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl}methyl}ethanaminium trifluoroacetate;

20 [5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-(1H-pyrrol-2-ylmethyl)methanaminium trifluoroacetate;

N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl}methyl}-4-chlorobenzenaminium chloride;

25 N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl}methyl}-3-chlorobenzenaminium chloride;

N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl}methyl}-2-chlorobenzenaminium chloride;

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- 3-bromo-N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl}methyl}benzenaminium chloride;
- 2-bromo-N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl}methyl}benzenaminium chloride;
- 5 N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl}methyl}-4-fluorobenzenaminium chloride;
- 10 N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl}methyl}-3-fluorobenzenaminium chloride;
- N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl}methyl}-2-fluorobenzenaminium chloride;
- 15 3-({[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}ammonio)pyridinium dichloride;
- 2-({[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}ammonio)-5-chloropyridinium dichloride;
- 20 4-bromo-N-{{5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl}methyl}benzenaminium chloride;
- 25 2-tert-butyl 4-methyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate};
- N-{{5-(tert-butoxycarbonyl)-4-ethyl-3-(methoxycarbonyl)-1H-pyrrol-2-yl}methyl}-4-pentylbenzenaminium trifluoroacetate;
- 30

- N- {[5-(tert-butoxycarbonyl)-4-ethyl-3-(methoxycarbonyl)-1H-pyrrol-2-yl]methyl}-
1,1'-biphenyl-4-aminium trifluoroacetate;
- 5 N- {[5-(tert-butoxycarbonyl)-4-ethyl-3-(methoxycarbonyl)-1H-pyrrol-2-yl]methyl}-
3,4,5-trimethoxybenzenaminium trifluoroacetate;
- 3-[4-({[5-(tert-butoxycarbonyl)-4-ethyl-3-(methoxycarbonyl)-1H-pyrrol-2-yl]methyl}
ammonio)phenyl]-5-methyl-4H-1,2,4-triazol-4-ium bis(trifluoroacetate);
- 10 [5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N- {[(2R)-5-
oxopyrrolidin-2-yl]methyl } methanaminium trifluoroacetate;
- diethyl 5- {[(4-chlorophenyl)amino]methyl }-3-methyl-1H-pyrrole-2,4-dicarboxylate;
- 15 N-benzyl[3,5-bis(ethoxycarbonyl)-4-methyl-1H-pyrrol-2-yl]methanaminium chloride;
- [3,5-bis(ethoxycarbonyl)-4-methyl-1H-pyrrol-2-yl]-N-(pyridin-2-ylmethyl)
methanaminium chloride;
- 20 [3,5-bis(ethoxycarbonyl)-4-methyl-1H-pyrrol-2-yl]-N-(2-chlorobenzyl)
methanaminium chloride;
- [3,5-bis(ethoxycarbonyl)-4-methyl-1H-pyrrol-2-yl]-N-(3-chlorobenzyl)
methanaminium chloride;
- 25 [3,5-bis(ethoxycarbonyl)-4-isopropyl-1H-pyrrol-2-yl]-N-(pyridin-2-ylmethyl)
methanaminium chloride;
- [5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]-N-(pyridin-2-
ylmethyl)methanaminium chloride;
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- N-{[3-[(benzyloxy)carbonyl]-5-(tert-butoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-4-methoxybenzenaminium trifluoroacetate;
- 5 N-{[5-(tert-butoxycarbonyl)-3-carboxy-4-ethyl-1H-pyrrol-2-yl]methyl}-4-methoxybenzenaminium trifluoroacetate;
- N-[(5-(tert-butoxycarbonyl)-4-ethyl-3-[(2-hydroxyethyl)amino]carbonyl)-1H-pyrrol-2-yl]methyl}-4-methoxybenzenaminium trifluoroacetate;
- 10 N-({5-(tert-butoxycarbonyl)-4-ethyl-3-[(ethylamino)carbonyl]-1H-pyrrol-2-yl}methyl)-4-methoxybenzenaminium trifluoroacetate;
- 2-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-[(4-methoxyphenyl)ammonio]methyl)-1H-pyrrol-3-yl]carbonyl}amino)methyl}pyridinium bis(trifluoroacetate);
- 15 4-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-[(4-methoxyphenyl)ammonio]methyl)-1H-pyrrol-3-yl]carbonyl}amino)methyl}pyridinium bis(trifluoroacetate);
- 20 N-({5-(tert-butoxycarbonyl)-4-ethyl-3-[(propylamino)carbonyl]-1H-pyrrol-2-yl}methyl)-4-methoxybenzenaminium trifluoroacetate;
- N-{[5-(tert-butoxycarbonyl)-4-ethyl-3-({[(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl]amino}carbonyl)-1H-pyrrol-2-yl]methyl}-4-methoxybenzenaminium
- 25 trifluoroacetate;
- 2-(2-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-[(4-methoxyphenyl)ammonio]methyl)-1H-pyrrol-3-yl]carbonyl}amino)ethyl}pyridinium bis(trifluoroacetate);
- 30 2-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-[(4-methoxyphenyl)ammonio]methyl)-

- 1H-pyrrol-3-yl)carbonyl]amino}methyl)-1H-imidazol-1-ium bis(trifluoroacetate);
- N-{[5-(tert-butoxycarbonyl)-4-ethyl-3-({[(5-oxopyrrolidin-2-yl)methyl]amino}carbonyl)-1H-pyrrol-2-yl]methyl}-4-methoxybenzenaminium trifluoroacetate;
- 5 3-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{[(4-methoxyphenyl)ammonio]methyl}-1H-pyrrol-3-yl)carbonyl]amino}methyl}pyridinium bis(trifluoroacetate);
- 2-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{[(4-methoxyphenyl)ammonio]methyl}-1H-pyrrol-3-yl)carbonyl]amino}methyl}-3H-benzimidazol-1-ium bis(trifluoroacetate);
- 10 N-[(5-(tert-butoxycarbonyl)-4-ethyl-3-{{[(isoxazol-3-ylmethyl)amino]carbonyl}-1H-pyrrol-2-yl)methyl}-4-methoxybenzenaminium trifluoroacetate;
- 15 N-{[3-({[2-(acetyl amino)ethyl]amino}carbonyl)-5-(tert-butoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-4-methoxybenzenaminium trifluoroacetate;
- N-{[5-(tert-butoxycarbonyl)-4-ethyl-3-({[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]amino}carbonyl)-1H-pyrrol-2-yl]methyl}-4-methoxybenzenaminium trifluoroacetate;
- 20 N-[(5-(tert-butoxycarbonyl)-4-ethyl-3-{{[(2-sulfoethyl)amino]carbonyl}-1H-pyrrol-2-yl)methyl}-4-methoxybenzenaminium trifluoroacetate;
- N-{[3-[(benzylamino)carbonyl]-5-(tert-butoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}-4-methoxybenzenaminium trifluoroacetate;
- 25 3-(2-{{[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{[(4-methoxyphenyl)ammonio]methyl}-1H-pyrrol-3-yl)carbonyl]amino}ethyl]-5-methyl-4H-1,2,4-triazol-4-ium bis(trifluoroacetate);

- 4-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-1H-pyrrol-3-yl)carbonyl]amino}methyl)-2-methyl-1,3-thiazol-3-ium bis(trifluoroacetate);
- 4-(2-{{[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-1H-pyrrol-3-yl)carbonyl]amino}ethyl)-1H-pyrazol-1-ium bis(trifluoroacetate);
- 5 1H-pyrazol-1-ium bis(trifluoroacetate);
- N-{{[(5-(tert-butoxycarbonyl)-4-ethyl-3-{{(1H-indol-6-ylmethyl)amino}carbonyl}-1H-pyrrol-2-yl)methyl]-4-methoxybenzenaminium trifluoroacetate;
- 10 6-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-1H-pyrrol-3-yl)carbonyl]amino}methyl)-2-methylimidazo[2,1-b][1,3]thiazol-7-ium bis(trifluoroacetate);
- 5-({{[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-1H-pyrrol-3-yl)carbonyl]amino}methyl)-3-methyl-4H-1,2,4-triazole-1,4-diium tris(trifluoroacetate);
- 15 1H-pyrazol-1-ium bis(trifluoroacetate);
- 4-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-1H-pyrrol-3-yl)carbonyl]amino}methyl)-1-methyl-1H-pyrazol-2-ium bis(trifluoroacetate);
- 20 N-{{[(5-(tert-butoxycarbonyl)-4-ethyl-3-({[(1-methyl-5-oxopyrrolidin-2-yl)methyl]amino}carbonyl)-1H-pyrrol-2-yl)methyl]-4-methoxybenzenaminium trifluoroacetate;
- 2-{{[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-1H-pyrrol-3-yl)carbonyl]amino}ethyl)-5-methoxy-3H-benzimidazol-1-ium bis(trifluoroacetate);
- 25 1H-pyrazol-1-ium bis(trifluoroacetate);
- 5-(2-{{[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-1H-pyrrol-3-yl)carbonyl]amino}ethyl)-1H-1,2,4-triazol-1-ium bis(trifluoroacetate);
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- 2-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-1H-pyrrol-3-yl)carbonyl]amino}methyl)-1-methyl-1H-imidazol-3-ium bis(trifluoroacetate);
- 5 6-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-1H-pyrrol-3-yl)carbonyl]amino}methyl)-2,3-dihydroimidazo[2,1-b][1,3]thiazol-4-ium bis(trifluoroacetate);
- 10 2-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-1H-pyrrol-3-yl)carbonyl]amino}methyl)-4-methyl-1H-imidazol-3-ium bis(trifluoroacetate);
- 15 2-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-1H-pyrrol-3-yl)carbonyl]amino}methyl)-8-methylimidazo[1,2-a]pyridin-4-ium bis(trifluoroacetate);
- 20 3-(1-{{[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-1H-pyrrol-3-yl)carbonyl]amino}ethyl)-5-methyl-4H-1,2,4-triazol-4-ium bis(trifluoroacetate);
- 25 2-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-1H-pyrrol-3-yl)carbonyl]amino}methyl)quinolinium bis(trifluoroacetate);
- 2-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-1H-pyrrol-3-yl)carbonyl]amino}methyl)-6-methylpyridinium bis(trifluoroacetate);
- N-{{[(5-(tert-butoxycarbonyl)-4-ethyl-3-{{[(4-methyl-1,3-thiazol-2-yl)methyl]amino}carbonyl]-1H-pyrrol-2-yl)methyl}-4-methoxybenzenaminium trifluoroacetate;
- 30 3-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-

1H-pyrrol-3-yl)carbonyl]amino}methyl)-6,7-dihydro-5H-cyclopenta[b]pyridinium
bis(trifluoroacetate);

3-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-1H-
5 pyrrol-3-yl)carbonyl]amino}methyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridinium
bis(trifluoroacetate);

N-{{[5-(tert-butoxycarbonyl)-4-ethyl-3-{{[2-(4-methyl-1,3-thiazol-5-yl)ethyl]
amino}carbonyl]-1H-pyrrol-2-yl]methyl}-4-methoxybenzenaminium trifluoroacetate;
10

3-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-1H-
pyrrol-3-yl)carbonyl]amino}methyl)-1-methylpiperidinium bis(trifluoroacetate);

4-(2-{{[5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}
15 methyl}-1H-pyrrol-3-yl)carbonyl]amino}-1-pyridinium-4-ylethyl)morpholin-
4-ium tris(trifluoroacetate);

4-(2-{{[5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}
methyl}-1H-pyrrol-3-yl)carbonyl]amino}-1-pyridinium-3-ylethyl)morpholin-
20 4-ium tris(trifluoroacetate);

N-{{[5-(tert-butoxycarbonyl)-4-ethyl-3-{{[5-fluoro-2-oxo-2,3-dihydro-1H-indol-3-yl]
methyl]amino}carbonyl]-1H-pyrrol-2-yl]methyl}-4-methoxybenzenaminium
trifluoroacetate;
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3-({[(5-(tert-butoxycarbonyl)-4-ethyl-2-{{(4-methoxyphenyl)ammonio}methyl}-
1H-pyrrol-3-yl)carbonyl]amino}methyl)-5-cyclopropyl-1H-pyrazol-1-ium
bis(trifluoroacetate);

- 2-([5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl)methyl] (hydroxy)ammonio)methyl]pyridinium bis(trifluoroacetate);
- 2-([5-(tert-butoxycarbonyl)-4-ethyl-2-([4-methoxyphenyl]ammonio)methyl]-1H-pyrrol-3-yl)carbonyloxy)methyl]pyridinium bis(trifluoroacetate);
- 5 N-[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-(2-phenylethyl)-1H-pyrrol-2-yl]methyl]-4-chlorobenzenaminium trifluoroacetate;
- 10 2-amino-N-[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl]glycinamide trifluoroacetate;
- N-[5-(tert-butoxycarbonyl)-4-ethyl-3-glycinamide-1H-pyrrol-2-yl]methyl]-4-methoxybenzenaminium trifluoroacetate;
- 15 or a stereoisomer thereof.

5. A compound selected from:

- 2-tert-butyl 4-ethyl 3-ethyl-5-([5-oxopyrrolidin-2-yl)methyl]amino)methyl]-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-ethyl 3-ethyl-5-([1H-indol-2-ylmethyl]amino)methyl]-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-ethyl 5-([3,4-dichlorophenyl]amino)methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-ethyl 3-ethyl-5-([4-methylphenyl]amino)methyl]-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-ethyl 3-ethyl-5-([4-hydroxyphenyl]amino)methyl]-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-ethyl 3-ethyl-5-([4-methoxyphenyl]amino)methyl]-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-([(4-chlorophenyl)(methyl)amino]methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-([(6-methylpyridin-2-yl)methyl]amino)methyl)-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-([(5-cyclopropyl-1H-pyrazol-3-yl)methyl]amino)methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-([(3,5-dimethyl-1H-pyrazol-4-yl)methyl]amino)methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-([(1H-indol-2-yl)methyl]amino)methyl)-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-([(1H-imidazol-2-yl)methyl]amino)methyl)-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-([(5-methyl-4H-1,2,4-triazol-3-yl)methyl]amino)methyl)-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-([(2-methylimidazo[2,1-b][1,3]thiazol-6-yl)methyl]amino)methyl)-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-([(4-methyl-1H-imidazol-2-yl)methyl]amino)methyl)-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-([(1-methyl-1H-imidazol-2-yl)methyl]amino)methyl)-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-([(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl]amino)methyl)-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-([(1H-1,2,4-triazol-5-yl)methyl]amino)methyl)-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-([(imidazo[2,1-b][1,3]thiazol-6-yl)methyl]amino)methyl)-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-([(6-chloro-1H-benzimidazol-2-yl)methyl]amino)methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-([(4-oxo-3,4-dihydrophthalazin-1-yl)methyl]amino)methyl)-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-([(1H-indol-6-ylmethyl)amino]methyl)-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-([(4-methyl-1,3-thiazol-2-yl)methyl]amino)methyl)-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-([(8-methylimidazo[1,2-a]pyridin-2-yl)methyl]amino)methyl)-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-([(1H-benzimidazol-2-ylmethyl)amino]methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-([(3-methylphenyl)amino]methyl)-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-([(4-isopropylphenyl)amino]methyl)-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-([(4-ethylphenyl)amino]methyl)-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-([(3,5-dimethylphenyl)amino]methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-([(3,4-dimethoxyphenyl)amino]methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-([(2-pyridin-2-ylethyl)amino]methyl)-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-([(1-methyl-1H-pyrazol-4-yl)methyl]amino)methyl)-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-([(4-ethoxyphenyl)amino]methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-([(3,4-dimethylphenyl)amino]methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-[(1,3-benzodioxol-5-ylamino)methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-([(4-isopropoxyphenyl)amino]methyl)-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-{{[(1,3-thiazol-4-ylmethyl)amino]methyl}}-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-{{[(1,3-thiazol-5-ylmethyl)amino]methyl}}-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-{{[(1,3-thiazol-2-ylmethyl)amino]methyl}}-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-{{[(isoxazol-5-ylmethyl)amino]methyl}}-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-{{[(1,5-dimethyl-1H-pyrazol-4-yl)methyl]amino}methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-{{[(4-tert-butylphenyl)amino]methyl}}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-{{[4-(dimethylamino)phenyl]amino}methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-{{[(2-methylphenyl)amino]methyl}}-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-{{[(2-methoxyphenyl)amino]methyl}}-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-{{[(4-propylphenyl)amino]methyl}}-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-{{[(2,5-dimethoxyphenyl)amino]methyl}}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-{{[(4-butylphenyl)amino]methyl}}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-{{[(3-hydroxy-4-methoxyphenyl)amino]methyl}}-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-[(1H-indol-4-ylamino)methyl]-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-[(1H-indol-6-ylamino)methyl]-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-[[(3-methoxypropyl)amino]methyl]-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-[(ethylamino)methyl]-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-[(butylamino)methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-[[(3-methoxyphenyl)amino]methyl]-1H-pyrrole-2,4-dicarboxylate;

4-([5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl)amino)butanoic acid;

2-tert-butyl 4-ethyl 3-ethyl-5-[(methylamino)methyl]-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-[(isobutylamino)methyl]-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-[(pentylamino)methyl]-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-([2-(aminosulfonyl)ethyl]amino)methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-[[(1H-pyrrol-2-ylmethyl)amino]methyl]-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-[[(4-chlorophenyl)amino]methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-[[(3-chlorophenyl)amino]methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-[[(2-chlorophenyl)amino]methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-[[(3-bromophenyl)amino]methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-[[(2-bromophenyl)amino]methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-[[(4-fluorophenyl)amino]methyl]-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-[[(3-fluorophenyl)amino]methyl]-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-[[(2-fluorophenyl)amino]methyl]-1H-pyrrole-2,4-

dicarboxylate;
2-tert-butyl 4-ethyl 3-ethyl-5-[(pyridin-3-ylamino)methyl]-1H-pyrrole-2,4-dicarboxylate;
2-tert-butyl 4-ethyl 5-[[[(5-chloropyridin-2-yl)amino]methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
2-tert-butyl 4-ethyl 5-[[[(4-bromophenyl)amino]methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
2-tert-butyl 4-methyl 3-ethyl-5-[[[(4-pentylphenyl)amino]methyl]-1H-pyrrole-2,4-dicarboxylate;
2-tert-butyl 4-methyl 5-[[[(1,1'-biphenyl-4-ylamino)methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
2-tert-butyl 4-methyl 3-ethyl-5-[[[(3,4,5-trimethoxyphenyl)amino]methyl]-1H-pyrrole-2,4-dicarboxylate;
2-tert-butyl 4-methyl 3-ethyl-5-[[[(4-(5-methyl-4H-1,2,4-triazol-3-yl)phenyl)amino]methyl]-1H-pyrrole-2,4-dicarboxylate;
2-tert-butyl 4-ethyl 3-ethyl-5-[[[(2R)-5-oxopyrrolidin-2-yl]methyl]amino]methyl]-1H-pyrrole-2,4-dicarboxylate;
diethyl 5-[(benzylamino)methyl]-3-methyl-1H-pyrrole-2,4-dicarboxylate;
diethyl 3-methyl-5-[[[(pyridin-2-ylmethyl)amino]methyl]-1H-pyrrole-2,4-dicarboxylate;
diethyl 5-[[[(2-chlorobenzyl)amino]methyl]-3-methyl-1H-pyrrole-2,4-dicarboxylate;
diethyl 5-[[[(3-chlorobenzyl)amino]methyl]-3-methyl-1H-pyrrole-2,4-dicarboxylate;
diethyl 3-isopropyl-5-[[[(pyridin-2-ylmethyl)amino]methyl]-1H-pyrrole-2,4-dicarboxylate;
2-tert-butyl 4-ethyl 3-ethyl-5-[[[(pyridin-2-ylmethyl)amino]methyl]-1H-pyrrole-2,4-dicarboxylate;
4-benzyl 2-tert-butyl 3-ethyl-5-[[[(4-methoxyphenyl)amino]methyl]-1H-pyrrole-2,4-dicarboxylate;
5-(tert-butoxycarbonyl)-4-ethyl-2-[[[(4-methoxyphenyl)amino]methyl]-1H-pyrrole-3-carboxylic acid;
tert-butyl 3-ethyl-4-[[[(2-hydroxyethyl)amino]carbonyl]-5-[[[(4-methoxyphenyl)amino]methyl]-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-4-[(ethylamino)carbonyl]-5-[[4-methoxyphenyl]amino]methyl}-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-[[4-methoxyphenyl]amino]methyl}-4-[[pyridin-2-ylmethyl]amino]carbonyl}-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-[[4-methoxyphenyl]amino]methyl}-4-[[pyridin-4-ylmethyl]amino]carbonyl}-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-[[4-methoxyphenyl]amino]methyl}-4-[(propylamino)carbonyl]-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-[[4-methoxyphenyl]amino]methyl}-4-[[5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl]amino]carbonyl)-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-[[4-methoxyphenyl]amino]methyl}-4-[[2-pyridin-2-ylethyl]amino]carbonyl)-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-4-[[1H-imidazol-2-ylmethyl]amino]carbonyl]-5-[[4-methoxyphenyl]amino]methyl}-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-[[4-methoxyphenyl]amino]methyl}-4-[[5-oxopyrrolidin-2-yl)methyl]amino]carbonyl)-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-[[4-methoxyphenyl]amino]methyl}-4-[[pyridin-3-ylmethyl]amino]carbonyl)-1H-pyrrole-2-carboxylate;

tert-butyl 4-[[1H-benzimidazol-2-ylmethyl]amino]carbonyl]-3-ethyl-5-[[4-methoxyphenyl]amino]methyl}-1H-pyrrole-2-carboxylate

tert-butyl 3-ethyl-4-[[isoxazol-3-ylmethyl]amino]carbonyl]-5-[[4-methoxyphenyl]amino]methyl}-1H-pyrrole-2-carboxylate;

tert-butyl 4-[[2-(acetyl amino)ethyl]amino]carbonyl)-3-ethyl-5-[[4-methoxyphenyl]amino]methyl}-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-[[4-methoxyphenyl]amino]methyl}-4-[[5-methyl-1,3,4-oxadiazol-2-yl)methyl]amino]carbonyl)-1H-pyrrole-2-carboxylate;

2-[[5-(tert-butoxycarbonyl)-4-ethyl-2-[[4-methoxyphenyl]amino]methyl]-1H-pyrrol-3-yl]carbonyl]amino]ethanesulfonic acid;

tert-butyl 4-[(benzylamino)carbonyl]-3-ethyl-5-[[4-methoxyphenyl]amino]methyl}-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-{{[2-(5-methyl-4H-1,2,4-triazol-3-yl)ethyl]amino}carbonyl)-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-{{[(2-methyl-1,3-thiazol-4-yl)methyl]amino}carbonyl)-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-{{[2-(1H-pyrazol-4-yl)ethyl]amino}carbonyl)-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-4-{{[(1H-indol-6-ylmethyl)amino]carbonyl}-5-{{[(4-methoxyphenyl)amino]methyl}-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-{{[(2-methylimidazo[2,1-b][1,3]thiazol-6-yl)methyl]amino}carbonyl)-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-{{[(5-methyl-4H-1,2,4-triazol-3-yl)methyl]amino}carbonyl)-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-{{[(1-methyl-1H-pyrazol-4-yl)methyl]amino}carbonyl)-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-{{[(1-methyl-5-oxopyrrolidin-2-yl)methyl]amino}carbonyl)-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-4-{{[2-(6-methoxy-1H-benzimidazol-2-yl)ethyl]amino}carbonyl)-5-{{[(4-methoxyphenyl)amino]methyl}-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-{{[2-(1H-1,2,4-triazol-5-yl)ethyl]amino}carbonyl)-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-{{[(1-methyl-1H-imidazol-2-yl)methyl]amino}carbonyl)-1H-pyrrole-2-carboxylate;

tert-butyl 4-{{[(2,3-dihydroimidazo[2,1-b][1,3]thiazol-6-ylmethyl)amino]carbonyl}-3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-{{[(4-methyl-1H-imidazol-2-yl)methyl]amino}carbonyl)-1H-pyrrole-2-carboxylate

tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-{{[(8-methylimidazo[1,2-a]pyridin-2-yl)methyl]amino}carbonyl)-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-{{[1-(5-methyl-4H-1,2,4-triazol-3-yl)ethyl]amino}carbonyl)-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-{{[(quinolin-2-yl)methyl]amino}carbonyl}}-1H-pyrrole-2-carboxylate;

tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-{{[(6-methylpyridin-2-yl)methyl]amino}carbonyl}}-1H-pyrrole-2-carboxylate;

Tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-{{[(4-methyl-1,3-thiazol-2-yl)methyl]amino}carbonyl}}-1H-pyrrole-2-carboxylate;

Tert-butyl 4-{{[(6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl)methyl]amino}carbonyl}-3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}}-1H-pyrrole-2-carboxylate;

Tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-{{[(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-3-yl)methyl]amino}carbonyl}}-1H-pyrrole-2-carboxylate;

Tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-{{[2-(4-methyl-1,3-thiazol-5-yl)ethyl]amino}carbonyl}}-1H-pyrrole-2-carboxylate;

Tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-{{[(1-methylpiperidin-3-yl)methyl]amino}carbonyl}}-1H-pyrrole-2-carboxylate;

Tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-{{[(2-morpholin-4-yl-2-pyridin-4-ylethyl)amino]carbonyl}}-1H-pyrrole-2-carboxylate;

Tert-butyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-4-{{[(2-morpholin-4-yl-2-pyridin-3-ylethyl)amino]carbonyl}}-1H-pyrrole-2-carboxylate;

Tert-butyl 3-ethyl-4-{{[(5-fluoro-2-oxo-2,3-dihydro-1H-indol-3-yl)methyl]amino}carbonyl}-5-{{[(4-methoxyphenyl)amino]methyl}}-1H-pyrrole-2-carboxylate;

Tert-butyl 4-{{[(5-cyclopropyl-1H-pyrazol-3-yl)methyl]amino}carbonyl}-3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}}-1H-pyrrole-2-carboxylate;

2-tert-butyl 4-ethyl 3-ethyl-5-{{[hydroxy(pyridin-2-yl)methyl]amino}methyl}}-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-(pyridin-2-ylmethyl) 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}}-1H-pyrrole-2,4-dicarboxylate;

2-tert-butyl 4-ethyl 5-{{[(4-chlorophenyl)amino]methyl}}-3-(2-phenylethyl)-1H-pyrrole-2,4-dicarboxylate;

2-amino-N-{{[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2-yl]methyl}}glycinamide;

4-(Carbamoylmethyl-carbamoyl)-3-ethyl-5-[(4-methoxy-phenylamino)-methyl]-1H-pyrrole-2-carboxylic acid tert-butyl ester;
or the pharmaceutically acceptable salt or stereoisomer thereof.

6. A TFA salt of the compound of Claim 1 selected from:

- 2-tert-Butyl 4-methyl 3-ethyl-5-{[(3-fluoro-4-methoxyphenyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate;
5 2-tert-butyl 4-methyl 3-ethyl-5-{[(2-methyl-1,3-benzothiazol-6-yl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate;
2-tert-butyl 4-methyl 3-ethyl-5-({[4-(1H-pyrazol-1-yl)phenyl]amino} methyl)-1H-pyrrole-2,4-dicarboxylate;
10 2-tert-butyl 4-methyl 3-ethyl-5-({[4-(2-oxoimidazolidin-1-yl)phenyl]amino} methyl)-1H-pyrrole-2,4-dicarboxylate;
2-tert-butyl 4-methyl 3-ethyl-5-({[4-(3-methyl-2-oxoimidazolidin-1-yl)phenyl] amino} methyl)-1H-pyrrole-2,4-dicarboxylate;
2-tert-butyl 4-methyl 3-ethyl-5-{[(3-fluoro-4-methoxyphenyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate;
15 2-tert-butyl 4-methyl 5-{[(cyclopropylmethyl)amino]methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
2-tert-butyl 4-methyl 3-ethyl-5-{[(4-phenoxyphenyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate;
20 2-tert-butyl 4-methyl 5-({[4-(aminocarbonyl) phenyl]amino} methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
4-({[5-(tert-butoxycarbonyl)-4-ethyl-3-(methoxycarbonyl)-1H-pyrrol-2-yl]methyl} amino)-2-hydroxybenzoic acid;
2-tert-butyl 4-methyl 5-[(cyclopropylamino)methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
25 2-tert-butyl 4-methyl 5-{[(6-chloro-1,3-benzothiazol-2-yl)amino] methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;

- 2-tert-butyl 4-methyl 5-[[[(2-chloropyrimidin-4-yl)amino]methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-[[[(2-chloro-6,7-dimethoxyquinazolin-4-yl)amino]methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 5 2-tert-butyl 4-methyl 5-[[[(5-bromopyridin-2-yl)amino]methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-[(pyrimidin-2-ylamino)methyl]-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-[(1,3-benzoxazol-2-ylamino)methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 10 2-tert-butyl 4-methyl 5-[[[(5-bromopyrimidin-2-yl)amino]methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-([[(5-chloro-2-(4H-1,2,4-triazol-4-yl)benzyl] amino)methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 15 2-tert-butyl 4-methyl 3-ethyl-5-([[(3-hydroxy-5-(hydroxymethyl)-2-methylpyridin-4-yl)methyl]amino)methyl]-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-([[(2-(3,4-dihydroxyphenyl)-2-hydroxyethyl]amino)methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-([[(2-(aminocarbonyl) cyclohexyl]amino)methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 20 2-tert-butyl 4-methyl 5-[[[(5-bromo-2-fluorobenzyl)amino]methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-([[(2-(3,4-dichlorophenyl) ethyl]amino)methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 25 2-tert-butyl 4-methyl 3-ethyl-5-([[(2-(1H-1,2,4-triazol-1-yl)ethyl] amino)methyl]-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-([[(4-(4-tert-butoxyphenyl)butyl]amino)methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-([[(1-(1H-benzimidazol-2-yl)ethyl]amino)methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 30

- 2-tert-butyl 4-methyl 3-ethyl-5-({[2-(1H-1,2,4-triazol-3-yl)ethyl] amino}methyl)-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[2-(4-methyl-1,3-thiazol-5-yl)ethyl] amino}methyl)-1H-pyrrole-2,4-dicarboxylate;
- 5 2-tert-butyl 4-methyl 3-ethyl-5-({[(1-morpholin-4-ylcyclopentyl)methyl] amino}methyl)-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[(2-piperidin-1-yl-2-pyridin-3-ylethyl) amino]methyl})-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[(3-phenylisoxazol-5-yl)methyl]amino}methyl)-1H-pyrrole-2,4-dicarboxylate;
- 10 2-tert-butyl 4-methyl 3-ethyl-5-({[(2-morpholin-4-yl-2-pyridin-2-ylethyl) amino] methyl})-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[(1-morpholin-4-ylcycloheptyl)methyl] amino} methyl)-1H-pyrrole-2,4-dicarboxylate;
- 15 2-tert-butyl 4-methyl 3-ethyl-5-({[(2,2,2-trifluoro-1-pyridin-3-ylethyl) amino]methyl})-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[(2-thien-2-yl-1,3-thiazol-4-yl)methyl] amino} methyl)-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[2-(5-phenyl-1H-1,2,4-triazol-3-yl) ethyl] amino}methyl)-1H-pyrrole-2,4-dicarboxylate;
- 20 2-tert-butyl 4-methyl 3-ethyl-5-({[(6-methoxy-1H-benzimidazol-2-yl)methyl] amino}methyl)-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-({[(2,3-dihydro-1,4-benzodioxin-2-yl)methyl] amino}methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 25 2-tert-butyl 4-methyl 3-ethyl-5-({methyl[(5-phenylisoxazol-3-yl) methyl]amino} methyl)-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-[(quinoxalin-2-ylamino)methyl]-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-({[(1,2-diphenylethyl) amino]methyl})-3-ethyl-1H-pyrrole-2,4-
- 30 dicarboxylate;

- 2-tert-butyl 4-methyl 5-{{[(2,2-diphenylethyl) amino]methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-[[{2-[4-(aminosulfonyl) phenyl]ethyl}amino) methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 5 2-tert-butyl 4-methyl 5-{{[(3,4-dihydroxybenzyl) amino]methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-{{[(1-benzylpiperidin-4-yl)amino]methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-[[{4-(aminosulfonyl) benzyl]amino}methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 10 2-tert-butyl 4-methyl 3-ethyl-5-{{[(2-morpholin-4-yl-2-pyridin-3-ylethyl) amino]methyl}-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-[[{1-(tert-butoxycarbonyl)-1H-indol-3-yl]methyl} amino]methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 15 2-tert-butyl 4-methyl 5-[[{[(4-benzylmorpholin-3-yl)methyl]amino}methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-[[{[(4-phenylmorpholin-3-yl) methyl]amino}methyl]-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-([methyl[(5-methyl-1H-indol-3-yl) methyl]amino]methyl)-1H-pyrrole-2,4-dicarboxylate;
- 20 2-tert-butyl 4-methyl 5-[(1,3-benzothiazol-2-ylamino)methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-{{[(1-phenyl-1H-tetrazol-5-yl)amino] methyl}-1H-pyrrole-2,4-dicarboxylate;
- 25 2-tert-butyl 4-methyl 3-ethyl-5-[[{(2R)-2-(3-fluorophenyl)-2-hydroxyethyl]amino}methyl]-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-[[{(2R)-2-(3-fluorophenyl)-2-hydroxyethyl][(2S)-2-(3-fluorophenyl)-2-hydroxyethyl]amino} methyl]-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-[[{(2R)-2-(4-fluorophenyl)-2-hydroxyethyl]amino}methyl]-1H-pyrrole-2,4-dicarboxylate;
- 30

- 2-tert-butyl 4-methyl 5-({bis[(2R)-2-(4-fluorophenyl)-2-hydroxyethyl]amino}methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[(2S)-2-(4-fluorophenyl)-2-hydroxyethyl]amino}methyl)-1H-pyrrole-2,4-dicarboxylate;
- 5 2-tert-butyl 4-methyl 3-ethyl-5-({[1-(4-fluorophenyl)-2-hydroxyethyl]amino} methyl)-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-({bis[(2S)-2-(4-fluorophenyl)-2-hydroxyethyl]amino}methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[(2S)-2-(4-fluorophenyl)-2-hydroxyethyl][1-(4-fluorophenyl)-2-hydroxyethyl]amino} methyl)-1H-pyrrole-2,4-dicarboxylate;
- 10 or a stereoisomer thereof.

7. A compound selected from

- 15 2-tert-Butyl 4-methyl 3-ethyl-5-({[(3-fluoro-4-methoxyphenyl)amino]methyl})-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[(2-methyl-1,3-benzothiazol-6-yl)amino]methyl})-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[4-(1H-pyrazol-1-yl)phenyl]amino} methyl)-1H-pyrrole-2,4-dicarboxylate;
- 20 2-tert-butyl 4-methyl 3-ethyl-5-({[4-(2-oxoimidazolidin-1-yl)phenyl]amino}methyl)-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[4-(3-methyl-2-oxoimidazolidin-1-yl)phenyl]amino}methyl)-1H-pyrrole-2,4-dicarboxylate;
- 25 2-tert-butyl 4-methyl 3-ethyl-5-({[(3-fluoro-4-methoxyphenyl)amino]methyl})-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-({[(cyclopropylmethyl)amino]methyl})-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[(4-phenoxyphenyl)amino]methyl})-1H-pyrrole-2,4-dicarboxylate;
- 30

- 2-tert-butyl 4-methyl 5-({[4-(aminocarbonyl) phenyl]amino} methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 4-({[5-(tert-butoxycarbonyl)-4-ethyl-3-(methoxycarbonyl)-1H-pyrrol-2-yl]methyl} amino)-2-hydroxybenzoic acid;
- 5 2-tert-butyl 4-methyl 5-[(cyclopropylamino)methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-{{[6-chloro-1,3-benzothiazol-2-yl]amino} methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-{{[2-chloropyrimidin-4-yl]amino}methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 10 2-tert-butyl 4-methyl 5-{{[2-chloro-6,7-dimethoxyquinazolin-4-yl]amino}methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-{{[5-bromopyridin-2-yl]amino}methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 15 2-tert-butyl 4-methyl 3-ethyl-5-[(pyrimidin-2-ylamino)methyl]-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-[(1,3-benzoxazol-2-ylamino)methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-{{[5-bromopyrimidin-2-yl]amino}methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 20 2-tert-butyl 4-methyl 5-({[5-chloro-2-(4H-1,2,4-triazol-4-yl)benzyl] amino} methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-{{[3-hydroxy-5-(hydroxymethyl)-2-methylpyridin-4-yl]methyl} amino)methyl}-1H-pyrrole-2,4-dicarboxylate;
- 25 2-tert-butyl 4-methyl 5-({[2-(3,4-dihydroxyphenyl)-2-hydroxyethyl]amino} methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-({[2-(aminocarbonyl) cyclohexyl]amino} methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-{{[5-bromo-2-fluorobenzyl]amino}methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 30

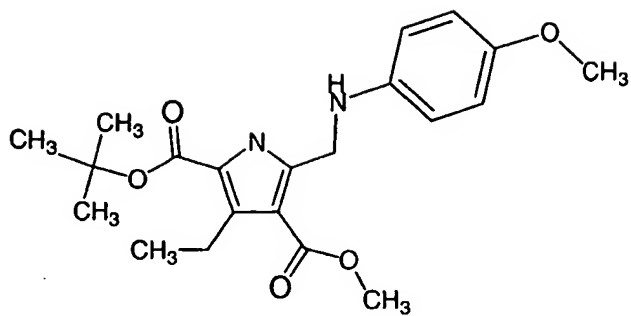
- 2-tert-butyl 4-methyl 5-({[2-(3,4-dichlorophenyl) ethyl]amino}methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[2-(1H-1,2,4-triazol-1-yl)ethyl] amino}methyl)-1H-pyrrole-2,4-dicarboxylate;
- 5 2-tert-butyl 4-methyl 5-({[4-(4-tert-butoxyphenyl)butyl]amino}methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-({[1-(1H-benzimidazol-2-yl)ethyl]amino}methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[2-(1H-1,2,4-triazol-3-yl)ethyl] amino}methyl)-1H-pyrrole-2,4-dicarboxylate;
- 10 2-tert-butyl 4-methyl 3-ethyl-5-({[2-(4-methyl-1,3-thiazol-5-yl)ethyl] amino}methyl)-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[(1-morpholin-4-ylcyclopentyl)methyl] amino}methyl)-1H-pyrrole-2,4-dicarboxylate;
- 15 2-tert-butyl 4-methyl 3-ethyl-5-({[(2-piperidin-1-yl-2-pyridin-3-ylethyl) amino]methyl}-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[(3-phenylisoxazol-5-yl)methyl]amino}methyl)-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[(2-morpholin-4-yl-2-pyridin-2-ylethyl) amino] methyl}-1H-pyrrole-2,4-dicarboxylate;
- 20 2-tert-butyl 4-methyl 3-ethyl-5-({[(1-morpholin-4-ylcycloheptyl)methyl] amino} methyl)-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[(2,2,2-trifluoro-1-pyridin-3-ylethyl) amino]methyl}-1H-pyrrole-2,4-dicarboxylate;
- 25 2-tert-butyl 4-methyl 3-ethyl-5-({[(2-thien-2-yl-1,3-thiazol-4-yl)methyl] amino} methyl)-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[2-(5-phenyl-1H-1,2,4-triazol-3-yl) ethyl] amino}methyl)-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({[(6-methoxy-1H-benzimidazol-2-yl)methyl] amino}methyl)-1H-pyrrole-2,4-dicarboxylate;
- 30

- 2-tert-butyl 4-methyl 5-{[(2,3-dihydro-1,4-benzodioxin-2-ylmethyl) amino]methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({methyl[(5-phenylisoxazol-3-yl) methyl]amino} methyl)-1H-pyrrole-2,4-dicarboxylate;
- 5 2-tert-butyl 4-methyl 3-ethyl-5-[(quinoxalin-2-ylamino)methyl]-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-{[(1,2-diphenylethyl) amino]methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-{[(2,2-diphenylethyl) amino]methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 10 2-tert-butyl 4-methyl 5-[(2-[4-(aminosulfonyl) phenyl]ethyl) amino] methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-{[(3,4-dihydroxybenzyl) amino]methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 15 2-tert-butyl 4-methyl 5-{[(1-benzylpiperidin-4-yl)amino]methyl}-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-({[4-(aminosulfonyl) benzyl]amino} methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-{[(2-morpholin-4-yl-2-pyridin-3-ylethyl) amino] methyl}-1H-pyrrole-2,4-dicarboxylate;
- 20 2-tert-butyl 4-methyl 5-[(1-(tert-butoxycarbonyl)-1H-indol-3-yl)methyl] amino] methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-({[(4-benzylmorpholin-3-yl)methyl]amino} methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 25 2-tert-butyl 4-methyl 3-ethyl-5-({[(4-phenylmorpholin-3-yl) methyl]amino} methyl)-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-({methyl[(5-methyl-1H-indol-3-yl) methyl]amino} methyl)-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-[(1,3-benzothiazol-2-ylamino)methyl]-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 30

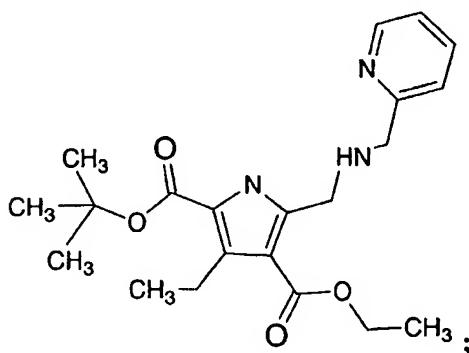
- 2-tert-butyl 4-methyl 3-ethyl-5-{{[(1-phenyl-1H-tetrazol-5-yl)amino] methyl}-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-{{[(2R)-2-(3-fluorophenyl)-2-hydroxyethyl]amino} methyl)-1H-pyrrole-2,4-dicarboxylate;
- 5 2-tert-butyl 4-methyl 3-ethyl-5-{{[(2R)-2-(3-fluorophenyl)-2-hydroxyethyl][(2S)-2-(3-fluorophenyl)-2-hydroxyethyl]amino} methyl)-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-{{[(2R)-2-(4-fluorophenyl)-2-hydroxyethyl]amino} methyl)-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 5-{{bis[(2R)-2-(4-fluorophenyl)-2-hydroxyethyl]amino} methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 10 2-tert-butyl 4-methyl 3-ethyl-5-{{[(2S)-2-(4-fluorophenyl)-2-hydroxyethyl]amino} methyl)-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-{{[1-(4-fluorophenyl)-2-hydroxyethyl]amino} methyl)-1H-pyrrole-2,4-dicarboxylate;
- 15 2-tert-butyl 4-methyl 5-{{bis[(2S)-2-(4-fluorophenyl)-2-hydroxyethyl]amino} methyl)-3-ethyl-1H-pyrrole-2,4-dicarboxylate;
- 2-tert-butyl 4-methyl 3-ethyl-5-{{[(2S)-2-(4-fluorophenyl)-2-hydroxyethyl][1-(4-fluorophenyl)-2-hydroxyethyl]amino} methyl)-1H-pyrrole-2,4-dicarboxylate;
- 20 or a pharmaceutically acceptable salt or stereoisomer thereof.

8. A compound selected from:

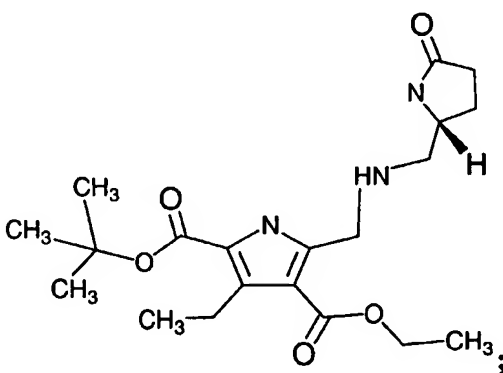
2-tert-butyl 4-methyl 3-ethyl-5-{{[(4-methoxyphenyl)amino]methyl}-1H-pyrrole-2,4-dicarboxylate



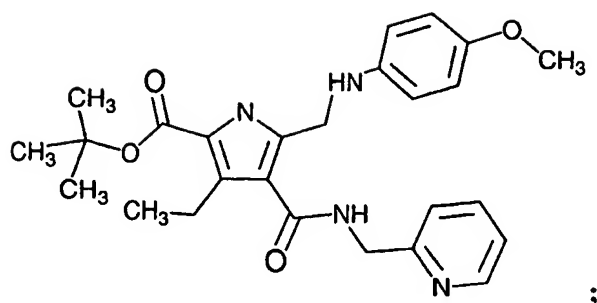
2-tert-butyl 4-ethyl 3-ethyl-5-[[[(pyridin-2-ylmethyl)amino]methyl]-1H-pyrrole-2,4-dicarboxylate



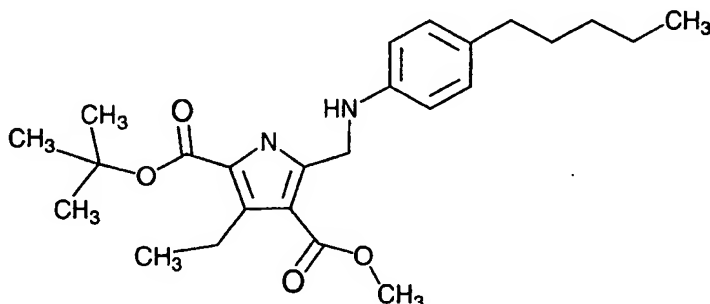
5 2-tert-butyl 4-ethyl 3-ethyl-5-[[[(2R)-5-oxopyrrolidin-2-yl]methyl]amino]methyl]-1H-pyrrole-2,4-dicarboxylate



tert-butyl 3-ethyl-5-[[[(4-methoxyphenyl)amino]methyl]-4-[[[(pyridin-2-ylmethyl)amino]carbonyl]-1H-pyrrole-2-carboxylate



2-tert-butyl 4-methyl 3-ethyl-5-([(4-penty]phenyl)amino]methyl)-1H-pyrrole-2,4-dicarboxylate



5 or the pharmaceutically acceptable salt or stereoisomer thereof.

9. A pharmaceutical composition which is comprised of a compound in accordance with Claim 1 and a pharmaceutically acceptable carrier.

10. A method of modulating the catalytic activity of protein kinases in a mammal in need thereof comprising contacting the protein kinase with a compound of Claim 1.

11. The method of Claim 10 wherein the protein kinase is an RTK.

15

12. The method of Claim 11, wherein the RTK is selected from IR, IGF-1R and IRR.

13. A method of treating or preventing a PK-related disorder in a mammal in need thereof comprising administering to said mammal a therapeutically effective amount of a compound of Claim 1.
- 5 14. A method of Claim 13, wherein the PK-related disorder is an IGF-1R-related disorder selected from:
- a) cancer,
 - b) diabetes,
 - c) an autoimmune disorder,
 - 10 d) a hyperproliferation disorder,
 - e) aging,
 - f) acromegaly, and
 - g) Crohn's disease.
- 15 15. A method of treating cancer in a mammal in need of such treatment comprising administering to said mammal a therapeutically effective amount of a compound of Claim 1.
- 20 16. A method of treating retinal vascularization comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1.
- 25 17. A method of treating cancer which comprises administering a therapeutically effective amount of a compound of Claim 1 in combination with a second compound selected from:
- 1) an estrogen receptor modulator,
 - 2) an androgen receptor modulator,
 - 3) retinoid receptor modulator,
 - 4) a cytotoxic agent,
 - 30 5) an antiproliferative agent,

- 5
- 6) a prenyl-protein transferase inhibitor,
 - 7) an HMG-CoA reductase inhibitor,
 - 8) an HIV protease inhibitor,
 - 9) a reverse transcriptase inhibitor, and
 - 10) an angiogenesis inhibitor.

18. The method of Claim 17, wherein the second compound is an estrogen receptor modulator selected from tamoxifen and raloxifene.
- 10 19. A method of treating cancer which comprises administering a therapeutically effective amount of a compound of Claim 1 in combination with radiation therapy.
- 15 20. The method of Claim 17 wherein radiation therapy is also administered.
- 20 21. A method of treating cancer which comprises administering a therapeutically effective amount of a compound of Claim 1 and paclitaxel or trastuzumab.
22. A method of treating or preventing cancer which comprises administering a therapeutically effective amount of a compound of Claim 1 and a GPIIb/IIIa antagonist.
- 25 23. The method of Claim 22 wherein the GPIIb/IIIa antagonist is tirofiban.
24. A method of treating or preventing cancer which comprises administering a therapeutically effective amount of a compound of Claim 1 in combination with a COX-2 inhibitor.
- 30

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
1 May 2003 (01.05.2003)

PCT

(10) International Publication Number
WO 2003/035615 A3

- (51) International Patent Classification⁷: **C07D 207/373, A61K 31/40** (74) Common Representative: **MERCK & CO., INC.**; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
- (21) International Application Number: **PCT/US2002/033920** (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (22) International Filing Date: 21 October 2002 (21.10.2002)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 60/343,119 25 October 2001 (25.10.2001) US (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- (71) Applicant (*for all designated States except US*): **MERCK & CO., INC.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): **TROTTER, B., Wesley** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **BELL, Ian, M.** [GB/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **ZARTMAN, C., Blair** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **LINDSLEY, Craig** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **ZHAO, Zhijian** [CN/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
- Published:
— with international search report
- (88) Date of publication of the international search report:
18 March 2004
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: **TYROSINE KINASE INHIBITORS**

(57) Abstract: The present invention relates to compounds that are capable of inhibiting, modulating and/or regulating signal transduction of both receptor-type and non-receptor type tyrosine kinases. The compounds of the instant invention possess a core structure that comprises a 2-carboxy pyrrole. The present invention is also related to the pharmaceutically acceptable salts, hydrates and stereoisomers of these compounds.



WO 2003/035615 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/33920

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07D 207/373; A61K 31/40

US CL : 548/533; 414/427

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 548/533; 414/427

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JACKSON et al. Purroles and Related Compounds. Part V. Syntheses of Some Pyrromethanes, Tripyrranes and Porphyrins. J. Chem. Soc. February 1965, pages 13281337, see entire document.	

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

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Date of the actual completion of the international search

27 June 2003 (27.06.2003)

Date of mailing of the international search report

10 JUL 2003

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